HHS Public Access

Author manuscript

Curr Clin Pharmacol. Author manuscript; available in PMC 2019 January 24.

Published in final edited form as:

Curr Clin Pharmacol. 2010 May ; 5(2): 96–114.

Clinical pharmacology and lesion penetrating properties of second- and third-line antituberculous agents used in the management of multidrug-resistant (MDR) and extensively-drug resistant (XDR) tuberculosis.

Véronique Dartois[1] and **Clifton E. Barry 3rd**[2]

[1]-Novartis Institute for Tropical Diseases, Biopolis, Singapore

[2]-Tuberculosis Research Section, National Institute of Allergy and Infectious Disease, National Institutes of Health, Bethesda, MD, USA.

Abstract

Failure of first-line chemotherapy to cure tuberculosis (TB) patients occurs, in part, because of the development of resistance to isoniazid (INH) and rifampicin (RIF) the two most sterilizing agents in the four-drug regimen used to treat primary infections. Strains resistant to both INH and RIF are termed multidrug-resistant (MDR). Treatment options for MDR patients involve a complex array of twenty different drugs only two classes of which are considered to be highly effective (fluoroquinolones and aminoglycosides). Resistance to these two classes results in strains known as extensively drug-resistant (XDR) and these types of infections are becoming increasingly common. Many of the remaining agents have poorly defined pharmacology but nonetheless are widely used in the treatment of this disease. Several of these agents are known to have highly variable exposures in healthy volunteers and little is known in the patients in which they must be used. Therapeutic drug monitoring (TDM) is infrequently used in the management of MDR or XDR disease yet the clinical pharmacokinetic studies that have been done suggest this might have a large impact on disease outcome. We review what is known about the pharmacologic properties of each of the major classes of second- and third-line antituberculosis agents and suggest where judicious use of TDM would have the maximum possible impact. We summarize the state of knowledge of drug-drug interactions (DDI) in these classes of agents and those that are currently in clinical trials. Finally we consider what little is known about the ability of TB drugs to reach their ultimate site of action - the interior of a granuloma by penetrating the diseased lung area. Careful consideration of the pharmacology of these agents is essential if we are to avoid further fueling the growing epidemic of highly drug-resistant TB and critical in the development of new antituberculosis drugs.

Keywords

clinical pharmacology; drug resistance; tuberculosis; antimycobacterial; antibiotics; PK/PD

INTRODUCTION

Multi-drug resistant tuberculosis (MDR-TB) is defined as a form of TB disease, caused by *Mycobacterium tuberculosis* (Mtb), which is resistant to at least isoniazid (INH) and rifampicin (RIF). These two drugs are considered to be the most effective anti-tuberculosis first-line drugs. INH and RIF are the pillars of a four-drug combination therapy recommended by the World Health Organization (WHO) to be taken daily for six to nine months (1). Treatment of MDR-TB is at least eighteen months long and usually involves a combination of four to seven so-called second-line drugs, most of which are less potent and cause more severe adverse effects than the first-line drugs (2). In addition, they are less affordable than first-line agents and therefore not always available in developing countries. Extensively drug-resistant tuberculosis (XDR-TB) combines MDR with additional resistances to the fluoroquinolones (FQs) and at least one injectable drug, i.e., aminoglycosides (AGs) or capreomycin (CAP). These are regarded as the most effective second-line drug classes (3). Treatment of XDR-TB is often exploratory, including antibiotics which have been developed for other disease indications, with little known regarding their clinical efficacy against pulmonary TB.

MDR-TB is an emerging public health threat, with half a million cases annually, or 5% of the global TB burden. Multiple factors have contributed to the emergence and spread of drug-resistant TB. Non-compliance on the part of TB patients and lack of systematic drug susceptibility testing (DST) in resource poor regions may be partly to blame, but this is compounded by inadequately executing the appropriate treatment of TB. XDR-TB has emerged from mismanagement of MDR-TB, treating tuberculosis with too few or poorly selected drugs, failing to understand the pharmacology of the handful of drugs that remain, and neglecting strict adherence measures.

A high degree of variability in MDR and XDR treatment outcome has been observed in different settings, from > 70% cure in a recent Peruvian study to almost complete failure in the XDRTB-HIV epidemic of Kwazulu-Natal (4–10). While part of this variability is due to differences in the definitions of treatment outcome (11), such a wide range of success rates indicates that there is room to improve individualized second- and third-line drug regimens. Careful analysis of pharmacology data available for all existing TB drugs along with therapeutic drug monitoring (TDM) can contribute to designing optimized drug regimens and stop further development and spread of TB drug resistance.

This review focuses on the clinical pharmacology of second- and third-line anti-TB drugs in use today, including pharmacokinetics (PK), degree of tissue penetration, clinical efficacy, and drug-drug interactions (DDI), along with critical gaps in our current understanding of these drug traits. Alternative drug delivery systems which could improve the pharmacokinetics of existing drugs are also summarized. The toxicities and adverse effects of these agents are well documented (12–17). Adverse effects and their management in clinical settings are not systematically addressed here. This review will instead focus on the clinical pharmacokinetic parameters of the twenty antibiotics used in the treatment of drug-resistant TB, including available data regarding tissue penetration. Knowledge of the

pharmacology of these drugs is fundamental to managing MDR and XDR-TB, improving treatment success rates and TB control worldwide.

Selection of a Drug Regimen for MDR- and XDR-TB.

In settings where complete DST is performed prior to treatment initiation, selection of a drug regimen is usually tailored to the patient's resistance profile. This customized design for treating MDR, and particularly XDR disease, is in contrast to general guidelines that are available from official sources such as the World Health Organization (17), the Center for Disease Control (18), and the State of California (15), to name a few. In settings where DST is not readily available in a timely fashion, a variety of preferred empiric retreatment regimens have been proposed (19–21). With few exceptions, the consensus opinion is that regimens tailored to a patient's DST results outperform standardized regimens (22–24).

A three-step treatment algorithm has been proposed for rational selection of drugs against MDR- and XDR-TB (25, 26). The first-line drugs to which the patient remains sensitive are considered in the first step of this algorithm, namely pyrazinamide (PZA) and ethambutol (EMB). Rifabutin (RBT) is often recommended to treat the small percentage of RIF-resistant patients who remain RBT sensitive (12–27%) (21, 27–29). One oral FQ (gatifloxacin, ofloxacin [OFX], levofloxacin [LEV] or moxifloxacin [MXF]) is also added, along with one injectable aminoglycoside (amikacin [AMI], streptomycin [STR], kanamycin [KAN]) or CAP. Next, the recommendations call for the use of at least two agents from the three remaining second-line anti-TB drug classes, including cycloserine (CS), thioamides (ethionamide [ETH] or prothionamide [PTH]), and p-aminosalicylic acid (PAS). These latter drugs are widely thought to be less potent than the FQs, aminoglycosides (AG) and RBT. Finally, third-line agents such as clarithromycin (CLA), amoxicillin-clavulanate, clofazimine (CLO), linezolid (LZD), metronidazole (MTZ) and more recently meropenem-clavulanate (30) have been suggested to have activity against *M. tuberculosis*. Although clinical data are presently limited, clinicians increasingly consider using them for XDR patients who are left without other treatment options. Phase II trials are currently ongoing with MTZ and LZD in South Korea, sponsored by the NIH/NIAID (www.clinicaltrials.gov). In addition to evaluating the effect of these agents against MDR and XDR-TB, the studies will provide critical information on their tolerability and pharmacokinetics in subjects with advanced disease.

A handful of new TB drug candidates are currently in development. Armed with novel mechanisms of action, these compounds all possess the potential to be effective against drug-resistant TB. These are the ATP synthase inhibitor TMC207, the nitroimidazoles PA824 and OPC-67683, the diamine SQ109 and the pyrrole LL3858, all of which have been recently reviewed (31, 32).

Overview of the Pharmacokinetics of Second- and Third-line Anti-tubercular Agents

The human pharmacokinetic (PK) parameters of second- and third-line drugs in plasma have been compiled in Table 1, along with their *in vitro* potency against drug-sensitive Mtb strains. Among the clinical development candidates, only TMC207 was included since human PK data are not yet available for the other compounds.

For the most part, the parameters summarized in Table 1 were derived from studies with healthy volunteers recruited in developed countries. The pharmacokinetics of antimycobacterial drugs in patients with MDR TB has been addressed in one small clinical study by Yew and coworkers (33) where twelve patients were included with each drug being taken by six of the twelve subjects. Yew's work reveals some intriguing trends with regard to absorption and half life of second-line drugs in MDR patients versus healthy volunteers. His results have been corroborated recently in a study showing that patients with tuberculosis or co-infected with HIV/AIDS have a decreased intestinal absorptive area that may relate to low serum concentrations of anti-tuberculosis drugs. Not surprisingly, patients in whom decreased absorption was most acute had developed drug resistance to a larger extent than those with normal intestinal absorption area (34). This observation highlights the need for large scale studies covering various ethnic groups in diseased populations in order to define 'normal ranges' that provide adequate treatment in patients with advanced disease and co-morbidities.

RBT is one of the best examples illustrating the pharmacological issues of antimycobacterial drugs used to treat complex TB disease (35). Among the most effective second-line drugs, RBT is one that presents many sources of inter-patient variability. Its absorption is affected by co-administered TB drugs, formulation, concomitant food intake (36), and disease states such as diabetes mellitus (37), HIV (38), and cystic fibrosis (39). RBT also induces its own hepatic metabolism, which is in turn inhibited by protease inhibitor-based antiretroviral therapy (40) and macrolide antibiotics (41), causing complex bidirectional interactions (detailed in a later section of this review). All these factors additively contribute to inter-individual variability of absorption, distribution, metabolism and excretion (ADME) properties. The resulting wide ranges in peak plasma concentration (C_{max}) and exposures of RBT have been shown to have a direct impact on treatment failure, relapse and acquired resistance (40).

Another drug with marked food effect and varying extent of absorption is PAS. It is more completely absorbed when given with a high fat meal, increasing the C_{max} by 50% and overall exposure by 70%. Overall, PAS pharmacokinetics show wide ranges of T_{max}, C_{max} and bioavailability due to mechanisms that are poorly understood. It also blocks absorption of vitamin B12 and can induce a malabsorption syndrome (42). Both PAS and RBT will be considered in more detail below but these examples illustrate the complexity of managing the polypharmacy of treatment of drug-resistant TB.

The Utility of Therapeutic Drug Monitoring for Managing MDR-TB

In general, second- and third-line medications are less effective, have more frequent side effects, have a narrower therapeutic/toxic effect ratio, and require a longer duration of treatment than first-line agents. TDM has been proposed as a means of obtaining plasma levels of a drug and modifying the dose or dosing interval based on the results to ensure that these levels remain within the therapeutic window (13, 66–68). This may help not only to maximize the chances of favorable clinical outcome but also to preclude the development of further resistance (69).

Because it is cost and labor intensive, TDM is often reserved for defined circumstances such as lack of clinical response, prolonged side effects, renal or hepatic dysfunction, suspected DDI, and co-morbidities such as HIV and diabetes which often cause poor absorption through the gastrointestinal tract (70, 71). A recent study conducted in twenty-one HIV-TB patients in the US (72) showed that 86% of the subjects had low serum concentrations of either INH, RIF, or both, 2 h after ingestion. In such an instance, TDM may be an effective tool to optimize therapy and overcome HIV-TB provided that higher drug doses are tolerated.

To ensure quality results and maximize cost effectiveness, sampling times must be carefully considered. For most drugs, it is recommended to obtain 2 h post-dose concentrations, corresponding to peak plasma levels or C_{max}. For a few drugs such as RBT and EMB, a 3 h timepoint may approximate the peak better, while the granular form of PAS has a peak plasma concentration 4 to 6 h post-dosing. However, low values at the theoretical C_{max} do not distinguish between delayed absorption (late peak but close to normal range) and malabsorption (low concentrations at all times). Therefore, a second sample is collected at 6 h post-dosing to differentiate between these two scenarios. Recommended drug-specific sampling times and expected concentration ranges have been previously reviewed (67, 73). Several other factors impact on the benefit and cost effectiveness of TDM: sample storage, performance of analytical methods, consideration of food effects, and proper action taken by the clinician in response to the results. An 11-step process has been proposed (74) to maximize not only patient care but also economic efficiency (75).

Knowledge of the concentrations required for effective therapy must be gained in order to optimize the benefits of TDM. Detailed pharmacokinetic-pharmacodynamic (PK/PD) data from human studies are lacking for many TB drugs (67). Precise targets for peak serum concentrations relative to minimum inhibitory concentrations (MIC), exposure relative to MIC or time above MIC are not available from human studies with many second- and third-line TB drugs. In the absence of such information, it is assumed that ‘normal’ ranges of serum levels, as defined in Phase I studies and outlined in Table 1, provide effective therapy because they are observed in patients who appear to be adequately treated. Very recently, pulmonary PK/PD modeling of RIF pharmacokinetics revealed that RIF concentrations measured in lung compartments following administration of the standard 600 mg dose failed to achieve acceptable target concentrations in 40 healthy volunteers (76).

Rather than consisting of a single numerical value of a serum drug concentration, TDM in drug-resistant TB should correlate bacteriological response, such as a decrease in bacterial load in sputum, to the ratio between drug exposure and MIC of the patient’s own TB isolate. This is due in part to strain variability in susceptibility to many of these agents, but this is further confounded by issues of subtle cross-resistances between drug classes. While the variation in MIC for first-line drugs is generally less than two-fold, for many of the second-line agents, this variation can be considerably larger and clinical break points have not been convincingly tested (77, 78). This has led some recent authors to argue for a pharmacogenomic approach, even for first-line agents (79). TDM benchmarked to the MIC of an individual patient’s isolate would ensure more effective use of the procedure by linking actual drug levels with response to therapy, allowing the construction of databases evaluating

whether ‘normal ranges’ do indeed provide (or not) satisfying clinical outcomes. One major limitation of TDM is that it only measures plasma levels, which do not reflect drug penetration within sequestered TB infection sites, where decreased pH and O2 content also affect the activity of some antibiotic classes such as the AGs (80).

TB and non-TB DDIs

TB chemotherapy is also significantly complicated by the fact that it frequently occurs in patients with other diseases such as HIV. TB also tends to occur frequently in patients that have many other underlying complications such as malnutrition, diabetes and generally poor health. Because of this, DDI are a hugely important, and vastly understudied, area. RIF is the antituberculous drug presenting the widest range of interference with the metabolism of other drugs (81). This is due to its inducing activity on enzymes of the cytochrome P-450 superfamily (CYP450), and on several other detoxifying enzymes or efflux systems. These interactions have been reviewed and updated regularly (81–83) and will not be described in detail here, since RIF is a first-line drug. However, RIF has several pharmacological interactions with second- and third-line agents which should be mentioned. Co-administered RIF reduces MXF exposure by 30% via induction of hepatic glucuronosyltransferase and sulphotransferase, the two enzymes primarily responsible for MXF liver metabolism (84–86). RIF also increases the CYP-mediated metabolism of CLA and other macrolides by inducing CYP3A4, which is responsible for the conversion of CLA to 14-hydroxyclarithromycin (87). Conversely, CLA is an inhibitor of CYP3A and therefore increases RBT exposure (41, 57). MTZ is thought to be metabolized by one or more unidentified CYP450 isomers. Hence, it has been suggested that DDI with MTZ be investigated on a case-by-case basis (88). Finally, RIF increases CYP-mediated metabolic clearance of TMC207, resulting in 50% reduction of TMC207 exposure when co-administered with RIF (89). Since MXF, CLA, MTZ and TMC207 primarily target MDR-TB disease, none of these interactions is expected to have major clinical implications. They remain important, however, because they also apply to RBT, another rifamycin with metabolic properties that are similar to those of RIF, though much less pronounced (90).

RBT is primarily metabolized by CYP3A4 (demethylation and hydroxylation) and by a cholinesterase to form a deacetylated product that has retained at least 50% of the activity of the parent drug against *M. tuberculosis* (91). RBT induces its own metabolism via both pathways (92). Because of its reduced pharmacological interferences, compared to RIF, it is often recommended in the treatment of TB-HIV with close monitoring of plasma drug levels and subsequent dose adjustments (12).

Very few studies have been conducted to investigate DDI between antiretrovirals and second- or third-line agents other than RBT. Several of these TB drugs were developed at a time when current knowledge of metabolic pathways and modern methods for detecting pharmacological interactions were not available. In many cases, DDI are considered unlikely to be clinically significant, though therapeutic monitoring of plasma drug levels is recommended. Clear evidence of interactions with HIV drugs exists for the macrolides, which increase the exposure of protease and reverse transcriptase inhibitors by inhibiting the CYP3A family (12). In addition to metabolic interactions, patients with HIV and other co-

morbidities such as diabetes mellitus can have impaired absorption through the gastro-intestinal tract, resulting in lower C_{max} and overall exposure. In the case of RBT, abnormally low plasma levels were shown to correlate with acquired resistance, treatment failure and relapse (40). The AGs as a class have low potential for DDI because they are not known to interfere with any of the CYP450 systems. They are mostly excreted unchanged.

Table 2 summarizes reasons for potential or demonstrated DDI between second- or third-line TB drugs as well as with other medications.

Tissue Penetration of Anti-TB Drugs

The issue of drug penetration at the site of action has been overlooked to a large extent. Anti-tuberculosis drugs do not exert their effect in the plasma, where their levels are traditionally measured, but in defined target tissues and lesions where they must be distributed. From a few studies published from the 1950s to the 1980s, it is believed that drug concentrations in these sequestered target sites can be substantially different from plasma concentrations, and could also be different for different drugs, even within the same class (100). Interestingly, drug-specific penetration has been demonstrated in abscesses and abscess fluid with significant differences observed within the same patient depending on abscess location, morphology and size (101, 102). This work is particularly relevant to the situation found in TB, given the structural similarities between abscesses and TB lesions: an outer fibrotic wall, inner layers of leukocytes and a central area of necrotic debris (103). Differential lesion-specific penetration is likely to be pronounced in TB disease where lesion diversity in size, location, structure and cellular/non-cellular content is remarkable.

The diversity of latent and active lesion types in pulmonary TB disease is impressive (104). Early granulomas are small and mainly cellular before evolving into closed, caseous, necrotic lesions that often develop a wall of fibrosis. These lesions may develop further due to liquefaction of the necrotic center ultimately leading to the formation of cavities open to an airway. On the other hand, effective containment by the immune system can lead to partial healing, fibrosis, calcification and the formation of consolidated, closed lesions. One commonly accepted paradigm is that these arrested granulomas contain the bacilli which are responsible for disease reactivation, though this remains to be formally demonstrated. Due to varying levels of vascularization and presence of physical barriers such as fibrosis and calcification, the extent of sequestration of the bacilli differs greatly between lesion types and lesion compartments.

The effect of such sequestration in other diseases can be dramatic in terms of drug levels at the infection site. This was nicely demonstrated with radiolabeled ceftriaxone in a rabbit model of staphylococcal endocarditis where this β-lactam was 20–30 times more concentrated at the periphery of fibrin-rich vegetations than in the core. Along with metabolic and immune factors, this lack of penetration was used to explain the requirement for high local drug concentrations in order to cure such infections (105, 106). It is likely that such phenomena may extend to other diseases presenting fibrotic lesions such as tuberculosis. Different drugs probably exhibit different lesion penetration properties and lesion-specific diffusion patterns may be observed for any given drug. In addition, micro-environmental conditions of low pH or low oxygen tension affect the metabolic and

replication status of the Mycobacteria, rendering them less susceptible to drug action. Finally, Mtb is a facultative intracellular pathogen. In other words, some of the bacteria are sequestered within the phagosome or phagolysosome of phagocytic cells, while others remain extracellular deep inside the necrotic core of large lesions. Taking these various phenomena into consideration, it is unlikely that each and every mycobacterial sub-population finds itself in the presence of drug levels that are sufficient to cause cell death or at least prevent growth in a sustained manner. Sub-therapeutic drug levels within TB lesions may thus contribute to the long treatment duration, treatment failure and development of drug resistance.

Unfortunately, clinical studies of drug penetration in pulmonary and other TB lesions are only limited to the two major first-line drugs INH and RIF, and date from the 1950s to 1980s. A study from 1953, with radioactive INH administered to three subjects with tuberculosis, indicated that INH and/or its metabolites were present in various lesion types at concentrations close to those seen in blood (107). In contrast, large scale Russian studies which included several hundred TB subjects undergoing lung resection (108, 109) reported INH and/or RIF levels in blood, healthy lung tissue, granulomas, cavities and pulmonary lymph nodes between 2 and 5 h post-dosing. This report found INH and RIF concentrations that were significantly lower in healthy and diseased tissue than in blood (Table 3). Similarly, a French study conducted on 34 pulmonary TB subjects (110) found caseum:lung levels in the range of 0.05 to 0.64 3 to 7 hours post-dose. In this study, lung levels were slightly higher than plasma concentrations with an average lung:serum ratio of 1.6 in the resected lung of these 34 subjects. In contrast, Kiss et al. (111) found lung tissue levels ranging between 30 – 60% of serum levels 2 to 9 hours post-dose. These values are in agreement with RIF lung levels observed in rabbits and non-human primates (personal communications with L. Via, J. Flynn, and our unpublished data). In all studies summarized above, except for the quantification of radioactive INH, the read-out was a biological assay which has intrinsic limitations in terms of accuracy, and may have been influenced by several confounding factors inherent to the biological matrix, the sample collection strategy and the bacterial indicator strains. Nevertheless, these studies indicate that penetration into diseased tissue and sequestered infection sites is both drug-specific and lesion-specific, in agreement with what is reported for non-TB drugs in abscess fluid. Preliminary results from animal experiments obtained by our groups have confirmed that different TB drugs have varying abilities to penetrate rabbit granulomas (unpublished data). There is clear need to refine and expand drug penetration studies in human TB lesions, employing state of the art technologies for the quantification of small molecules.

The penetration of some second- and third-line TB drugs in epithelium lining fluid (ELF), broncho-alveolar lavage (BAL) or sputum, and alveolar macrophages (AM) has been determined to some extent. Though this only provides a partial picture of overall drug distribution between blood, lung and closed lesions or open cavities, valuable information can be gained regarding the relative ability of drugs from different classes to penetrate extra-vascular and intracellular compartments. These numbers are summarized in Table 4, along with intracellular:extracellular ratios. It should be noted that sampling and drug quantification in bronchial secretions is fraught with methodological pitfalls (112, 113), and that care should be taken when interpreting the data. Overall however, a few key points

emerge from available data. Perhaps most importantly, one should not take for granted the often-accepted idea of a complete and lasting equilibration between blood and tissue for small molecules. Different drugs have different abilities to penetrate tissues, bronchial secretions and macrophages. One of the best 'penetrators' of cells and tissues appears to be CLA, which may compensate for its high MIC ((114) and Table 1). At the opposite end of the spectrum, the β-lactams distribute poorly in the various tissues analyzed and within cells (114).

The AGs in general are relatively polar molecules with poor absorption properties and virtually no oral bioavailability. While there are no data available on the intrapulmonary PK of KAN, AMI or STR, sputum and ELF concentrations of tobramycin have been extensively measured in cystic fibrosis patients. When given intravenously, tobramycin did not reach sputum in concentrations sufficient to inhibit or kill the relevant pathogens (115, 116). Nevertheless, the drug appeared to accumulate in sputum at significantly higher levels upon repeated administration for 2 or more weeks (117). If this holds true for AMI, such slow sputum penetration may be partially responsible for its failure to decrease sputum bacterial counts in early bactericidal activity (EBA) studies (118). Rifamycins as a class show favorable intracellular partitioning (35). With its large volume of distribution (Table I) and 9:1 intracellular-to-extracellular ratio, RBT is expected to accumulate in lung tissue and within cells. Though experimental and clinical data of RBT distribution in tissues and fluids are still lacking, a recent study demonstrated that pulmonary concentrations of RIF in ELF and AM are insufficient to provide satisfactory target attainment in TB patients (76). The results clearly support the need to evaluate higher doses of rifamycins in clinical trials, despite the fact that this class of compounds displays reasonably good penetration in lung compartments.

It is generally recognized that the logP (the octanol:water partition coefficient) of a drug contributes to its ability to leave the blood compartment and penetrate into tissues and cells, and that high molecular weight negatively affects passive diffusion through cells. The data presented in Table 4 suggest a trend in that direction, though it is clear that molecular weight and calculated LogP alone are not sufficient to predict distribution into cells and tissue. Many confounding factors influence tissue distribution and intracellular accumulation. First, plasma protein binding plays a major role in tissue penetration, in a manner which is difficult to predict since the protein content of the various compartments involved is often unknown. One exception is ELF where protein levels are thought to be low and free antibiotic concentrations are generally regarded as equivalent to the measured total concentration (113). In general, high serum protein binding hinders tissue penetration (119). Second, specific cell types show different intracellular:extracellular distribution ratios due to varying levels of active transport, efflux, intracellular binding and other much less well understood phenomena. One striking example is that of MXF accumulation in unstimulated versus differentiated macrophages, as MXF has more favorable distribution properties in activated macrophages (120). LEV on the other hand, another FQ, exhibits no difference whatsoever in penetration of both cell types (120). Consequently, values of intracellular drug accumulation should be compared with caution across studies. Finally, PZA, ETH, and PTH, as well as the nitroimidazole drug candidates, are prodrugs which are converted intracellularly to their less permeable active principle(s) by mycobacterial enzymes, causing

accumulation of these activation products within mycobacterial cells (121–123). These bacterial cells can be either extracellular or located within macrophages and other immune cells. Depending on the distribution and density of metabolically active bacilli, which vary widely between lesion types and lesion compartments (124), active pro-drug metabolites will be generated and accumulate to different degrees in different regions of the diseased lung. Therefore, studies that aim at understanding the partitioning of PZA or thioamides between blood, body fluids and macrophages should reproduce the situation found *in vivo* (i.e. presence of the pathogen responsible for pro-drug conversion) and include quantification of the conversion products in the various compartments.

Given the varying abilities of different drugs to penetrate lung lesions and bronchial secretions, it appears that meaningful PK/PD indices should include drug levels at the site of infection in addition to plasma PK. However, as seen in Tables II and III, available human data are still too sparse and anecdotal to systematically compute PK/PD parameters based on ELF or lesion levels. Advantage should be taken of animal models, such as the non-human primates and the rabbit, where the diversity and size of the lesions best reproduces the situation seen in humans. Systematic determination of penetration ratios for all TB drugs in closed necrotic lesions and cavities is required to (i) establish pharmacokinetic models of drug diffusion in each lesion type, (ii) identify lesions that are most resistant to drug penetration, and (iii) determine whether sub-therapeutic drug levels within lesions and lesion compartments may contribute to treatment length, treatment failure and emergence of drug resistance. Clinical studies with TB patients undergoing lung resection would be helpful to validate the results obtained in animal models. Because lesion sampling requires animal sacrifice or invasive surgical procedures in the clinic, validated surrogate markers of drug content in lesions and cavities, such as sputum drug levels for example, are needed.

Pharmacodynamics and Clinical Efficacy of Second- and Third-Line Agents

Because pulmonary TB strictly requires treatment with combination therapies, it is extremely challenging to reliably quantify the clinical efficacy of individual TB drugs. The only circumstance under which monotherapy has been ethically justified is the evaluation of EBA during the first 7 to 14 days of treatment in newly diagnosed TB patients. Available EBAs of 2nd and 3rd line agents are summarized in Table 5. One intrinsic limitation of EBA is that the results only reflect the ability of a given drug to cause a decrease in the number of culturable bacteria present in sputum (145). This bacterial population is thought to originate primarily from open cavities and may therefore reflect primarily actively replicating organisms within an oxygen rich environment, although at many levels these facts remain speculative. Hence, EBA does not measure the potential of a drug for killing non-growing bacteria or sterilizing closed lesions which never come into contact with sputum.

For evaluating the utility of individual drugs in the treatment of drug resistant disease, the options available to clinical investigators are limited since a typical MDR-XDR regimen contains at least 4 to 6 antibiotics. Ideally, placebo-controlled trials are designed where the contribution of the investigational drug is evaluated by adding it to an individualized second-line regimen. The control arm receives placebo in addition to a similar individualized regimen. Randomization ensures that potential confounding factors are equally distributed

between the two study arms. This type of study is currently being conducted with MDR-TB patient populations for MTZ, LZD (ClinicalTrials.gov numbers NCT00425113 and NCT00727844) and the Phase II clinical candidate TMC207 (65). But many more such studies are needed to benchmark the clinical efficacy of the so-called 'old' drugs like PZA, PAS, CS, ETH, PTH and CLO using standardized definitions of outcome measures (146, 147). Newer and more well-characterized drugs, such as the FQs, AGs and CAP, have not been evaluated in randomized and placebo-controlled MDR-TB trials, yet they are 'automatically' included in standard MDR combination therapies. In the absence of controlled trial data, some information on the respective contribution of different drug classes can be obtained from multivariate analyses of correlations between drug resistance and treatment outcome in case studies. For example, the use of FQs is consistently found to be associated with favorable microbiologic and clinical outcomes (3). A systematic analysis of all available clinical trial data would be key to reassess the scientific evidence for what we currently "know" about response to second- and third-line drug treatment in pulmonary TB.

A. Second-line drugs considered most effective

The Fluoroquinolones: Fluoroquinolones (FQs), both first and newer generations, are considered highly effective against Mtb. Their superiority over most other second-line agents is due in part to their bactericidal activity against TB, with ratios of minimum bactericidal concentration (MBC) to MIC generally between 2 and 4 (158) (Table I). FQs are also characterized by reliable and reproducible DST results, a key advantage in optimizing treatment success for MDR-TB. In addition to good potency *in vitro*, they achieve high drug levels in tissues, bronchial secretions, macrophages and neutrophils (159) (Table 4). Owing to their bactericidal activity and good tissue distribution, they display better EBA than other second-line agents for which this has been measured (151, 160). Consequently, MXF was investigated as first-line substitution in several large scale trials, replacing either INH or EMB, with the objective to shorten standard TB therapy. These studies have thus far provided only mixed results with some of them still in the recruiting phase. TBTC Study 27 (http://clinicaltrials.gov/ct2/show/NCT00164463) compared MXF with EMB and found that culture conversion occurred more rapidly in patients treated with MXF; however, the proportions of patients with negative cultures were similar in both arms after 8 weeks (161). Recently, a Johns Hopkins study (162) showed that MXF versus EMB improved culture conversion by almost 20% in the first 8 weeks of treatment. In the OFLOTUB study, OFX when substituted for EMB in a conventional combination regimen, slightly accelerated the killing of Mtb in sputum during the initial phase of treatment (163). Overall, in drug-susceptible TB, the impact of adding a FQ to a RIF-containing regimen does not appear to be dramatic. The situation is markedly different in MDR-TB, where both INH and RIF are absent from drug regimens. In multivariate analyses of case studies, the use of FQs is consistently found to be associated with favorable outcome (3, 11, 19). Similarly, resistance to, or prior use of, FQs is most often correlated with poor treatment outcome. Unfortunately, FQs are used in the treatment of a vast range of infectious diseases, most likely for reasons similar to those described above, i.e. bactericidal properties along with attractive pharmacokinetics and tissue penetration. In addition, they are available over the counter in many developing countries, leading to high rates of pre-existing drug resistance in some clinical isolates (9).

In the absence of rigorously controlled clinical trials on the efficacy of adjunctive FQ against drug resistant TB, there is no agreement on the best FQ for MDR-TB treatment. However, if one combines characteristics of *in vitro* potency and clinical pharmacokinetics, MXF seems to score slightly better than other FQs in each category. More explicitly, MXF has MIC and MBC similar to other FQs but a lower mutant prevention concentration (MPC) (164); its overall drug exposure in plasma is higher, as well as its ELF:plasma and AM:plasma ratios (Table I & III); and MXF is preferentially taken up by activated macrophages in contrast to LEV (120). It is thus expected to achieve higher AUC/MIC or AUC/MPC at the site of infection. In the mouse model of infection, AUC/MIC was found to be the PK/PD index driving FQ efficacy (165), suggesting that total exposure over time should be maximized.

The injectables: Aminoglycosides and Capreomycin: STR was among the first antibiotics to be used in pulmonary TB in the late 40's. Though the designs of clinical trials were less controlled and rigorous than contemporary trials, the efficacy and treatment response to STR were clearly established in large patient cohorts(166). However, therapy duration was 18 to 24 months, the drug had to be injected several times a day, and resistance was quick to emerge in most cases since it was used as a monotherapy (167). For these reasons, STR was replaced with more potent and orally bioavailable agents as they were developed.

Other than their *in vitro* bactericidal activity (Table I) and the fact that STR was proven efficacious in the clinic in the early days of anti-TB therapy, there is a little convincing justification in the scientific literature for the use of newer AGs, namely AMI and KAN, against MDR-TB. Clinical reports that they contribute appreciably to treatment of MDR-TB are still anecdotal. Despite AMI's strong extracellular bactericidal activity *in vitro*, EBA studies revealed either borderline or no significant change in sputum counts (118, 168), comparable to what was observed previously for STR (153). In one study where resistance to second-line injectables was correlated with treatment outcome, resistance to CAP - which is often misclassified as an AG - was an independent predictor for therapy failure, while resistance to either KAN or AMI did not appear to be as important an indicator of poor prognosis (6). Recently, resistance to injectables other than STR was not associated with poor treatment outcome in a Korean study including 211 patients (169). Other reports on the link between susceptibility to injectibles and long-term prognosis suggest a positive correlation, but the distinction between CAP and the AGs is not clearly made (4, 170). As mentioned earlier, placebo-controlled trials investigating the utility of adjunctive AG in MDR-TB have not been conducted.

The moderately convincing reports on the clinical efficacy of AMI and KAN against MDR-TB might not be totally surprising in view of their pharmacokinetic and physico-chemical properties. They have markedly reduced antibacterial activity at pH 6.0 and no activity at pH 5.0 or below (143, 171, 172). Hence they likely have a limited ability to kill bacilli present in necrotic caseous lesions, thought to be acidic with pH ranging from 5.5 to 6.0 (D. A. Mitchison, personal communication and (173)). Indirect evidence that lesions are slightly acidic reside in the observation that (i) PZA has a high sterilizing potential while STR is a poorly sterilizing drug (145), (ii) inflammation is recognized to produce local acidity due to accumulation of CO2 and lactic acid and (iii) pH ranging from 5.5 to 7.2 have been measured in abscess fluid (102), a matrix which has many similarities with caseum. A

similar pH range is found within the phagolysosome of activated macrophages, another niche for mycobacterial subpopulations. AGs also interact with sputum components that interfere with their activity: binding to mucin and ions was shown to cause a 10- to 25-fold increase in MIC in the presence of purulent sputum (117, 174). Thus high sputum concentrations may be required for the AGs to effectively kill extracellular bacilli. Unfortunately, sputum concentrations have only been determined for tobramycin in cystic fibrosis patients, where the sputum:serum ratio was low around 0.1 to 0.2 following single dose (116) (Table 4). The AGs as a class are polar molecules with very low cLogP, which could explain their low volume of distribution (Table I). Despite the fact that tobramycin seems to slowly accumulate in sputum after 2–3 weeks (117), AG levels in bronchial secretions and lesions may not reach peak concentrations sufficient to effectively kill extracellular and intracellular mycobacteria since the PK/PD index driving efficacy of the AGs is C_{max}/MIC (175).

CAP, on the other hand, doesn't suffer from pH dependency and has been shown to kill non-replicating Mtb bacilli (176). There is a growing interest in developing an inhalation formulation for CAP, which may overcome the problem of suboptimal tissue penetration, help lower overall dosing while achieving high peak concentrations at the site of infection, minimize systemic drug concentrations and adverse effects, and yield an entirely 'oral' regimen to improve global compliance (MEND, http://www.medicineinneed.org/mend-biotech-development.html). Promisingly, inhaled AMI or KAN used as adjunctive salvage therapy in a small exploratory study helped most patients with persistent culture positive sputum to convert to negativity within two months (177).

Pyrazinamide: PZA is one of the most complex and least well-understood TB drugs. The mechanisms behind its activity against certain bacterial populations and not others remain hypothetical. *In vitro*, it is active at pH 5.5 and below (172) and it has been shown to have some killing activity when bacterial metabolism is low. PZA is the opposite of conventional antibiotics in that it is less active against young, growing bacilli than against older, non-growing 'persisters' (178). These observations lead to the hypothesis that it might effectively target mycobacteria present in the lysosome and phagolysosome of activated macrophages within lesions. Attempts to confirm this *in vitro* led to conflicting reports (179–181), likely due to differences in cell lines, experimental design and drug concentrations used (K. Pethe, personal communication). Nevertheless, adjunctive PZA appears to consistently increase the sterilizing potential of many drug regimens. Its addition to the INH-RIF combination made it possible to complete a successful treatment in six months with significantly lower relapse rates (182–184). Unlike many other TB drugs, it maintains a slow but constant EBA throughout the entire 14 days of monotherapy (145). PK/PD experiments in the acute mouse model indicated that time above MIC (T>MIC) was the best predictor of bacterial load reduction. Caution should be taken before extrapolating this to humans, however, since bacilli are mostly found within macrophages in the mouse model, much more so than in established human disease.

B. The 'old' static drugs with narrow therapeutic window—This description usually refers to PAS, CS, ETH, PTH and CLO, discovered between 1943 and 1957. They

are mainly specific for Mycobacteria and were widely used before the advent of the more potent first-line drugs of today, INH and RIF. Therefore, resistance is not as common as for drugs which were used for decades to treat not only TB but other infectious diseases. A typical MDR or XDR drug regimen often contains two depending on the patient's drug resistance profile, with the notion that they are static (rather than cidal) and slow to act, with the possible exception of CLO. Little if anything is known about their respective activity against the various sub-populations of bacilli.

PAS was developed and tested as a monotherapy almost immediately following STR in the late 40's. While clinical response was not as good as for STR, resistance was much slower to arise, PAS proved less toxic and orally bioavailable. The two drugs were soon used in combination to prevent emergence of resistance, with treatment duration of 18–24 months to maximize the chances of relapse-free outcome (185, 186). Thus PAS has a well documented clinical efficacy against pulmonary TB, combined with relatively infrequent resistance, justifying its use as a static 2nd line drug. But as is the case of most old drugs, it is overall poorly characterized in terms of PK and the effect of micro-environmental conditions.

CLO is primarily used to treat leprosy, and its utility in the treatment of TB remains controversial. Its PK profile is peculiar, with slow and variable absorption, and a very long terminal half-life of 70 days. It distributes favorably into tissues and accumulates in macrophages to very high levels, which can lead to organ damage caused by crystal deposition (187, 188). There are no reports of its clinical efficacy against tuberculosis but it has documented efficacy against selected non-TB Mycobacteria (189). Further pre-clinical and clinical testing could bring an additional agent to the limited MDR-XDR panoply.

C. Third-line drugs under exploratory use for TB—A number of antibiotics, which are not normally part of anti-TB regimens, are increasingly used off-label for highly resistant patients with few or no other alternatives, essentially in countries or by patients with sufficient economic resources. Among these are CLA, LZD, MTZ, and amoxicillin-clavulanate. All these antibacterials have documented *in vitro* activity against Mtb (190–193) but reports of their clinical efficacy are mostly anecdotal with no controlled trial data available so far in TB patients.

In a drug-sensitive cohort, LZD demonstrated a modest EBA against rapidly dividing bacilli in patients with cavitary pulmonary tuberculosis during the first 2 days of administration, but little extended EBA over the subsequent 5 days (157). Though small and not placebo-controlled, a number of very recent studies have concluded that LZD is reasonably tolerated at 600mg daily, consistently lowers bacillary loads, and shows promising efficacy for the treatment of difficult MDR cases (194–196). A randomized, controlled Phase IIa study has been initiated to evaluate the effectiveness and tolerability of LZD in XDR-TB patients, based on encouraging clinical experience and case reports of patients with persistently positive sputum cultures (191, 197, 198).

Several β-lactam/β-lactamase inhibitor combinations have been examined for their potential against XDR-TB (199, 200). Recent enzymatic and mechanistic studies of meropenem and clavulanate with the Mtb β-lactamase have revealed *in vitro* properties that could be

exploited in the treatment of MDR and XDR-TB (30). Two reports of EBA have been published for amoxicillin-clavulanate, one where its activity was significant and comparable to that of FQs (156) and another one where the treated and placebo groups could not be distinguished (155). In the latter case, the authors point to the very low sputum:plasma ratio reported previously (136, 137, 141) and summarized in Table 4. Interestingly, patients in the study which gave positive EBA received 3 times daily a dosage of 1 g / 250 mg of amoxicillin/clavulanate, while a once daily dosage of 3 g / 750 mg was administered in the other study. Given that the PK/PD driver of efficacy for the β-lactams is known to be T>MIC, the negative results observed in (155) could be due to much lower T>MIC in the once-daily dosing design. The weak points of the β-lactams are their relatively poor tissue distribution, short half-life and lack of intracellular activity (114). In addition, several of them are not orally bioavailable. However, the sterilizing activity of meropenem-clavulanate against multiplying Mycobacteria and its inhibitory activity in anaerobically grown cultures (30), along with the scarceness of therapeutic options for XDR patients, undoubtedly warrant further investigation of their effectiveness in this patient population.

The history of MTZ for TB originates from the 1950s, when it was postulated that bacilli found in inflammatory and necrotic tissues within the human host have adapted to a low-oxygen microenvironment induced by granuloma formation (201, 202). These early observations were confirmed in animal models through labeling studies using the oxygen-sensitive probe pimonidazole (104, 203). An *in vitro* model of anaerobic non-replicating persisters was developed where the bacilli become phenotypically resistant to front-line antituberculosis agents (204), while acquiring a unique susceptibility to MTZ, a drug specifically used against anaerobes (192). Based on these observations, a clinical study has been initiated, where the efficacy of adjunctive MTZ to second-line agents is evaluated in MDR patients, with the idea that MTZ should inhibit or kill anaerobic subpopulations of bacilli which are otherwise resistant to anti-TB therapy (www.clinicaltrials.gov ID NCT00425113).

D. A promising drug in clinical development - TMC207—TMC207 is a first-in-class investigational anti-TB agent with a novel mechanism of action and potent preclinical activity against susceptible and resistant TB isolates (205). Interestingly, it is synergistic with PZA in the mouse, possibly due to the fact that they both interfere with membrane potential and electron transport. The ATP synthase inhibitor seems to have favorable tissue penetration, with a lung-to-plasma ratio of 22:1 in the mouse. In a Phase IIa trial where patients received a 5-drug MDR regimen plus either placebo or TMC207 for 8 weeks, conversion to culture-negative sputum was 8.7% in the control group versus 47.5% in the TMC207 treated group, with no serious adverse events attributable to the study drug (65, 206). The development of TMC207 has generated considerable enthusiasm for potential use against non-TB Mycobacterial (NTM) diseases since it has very good activity against most NTM, which are a significant problem in the Western world, essentially in immuno-compromised patient populations (elderly, HIV, etc.). Currently, there are no cidal drugs against most NTMs, and a typical treatment is 9 to 18 months long with average cure rates lower than those of MDR-TB. As mentioned earlier, TMC207 is metabolized by CYP3A4 which is in turn induced by RIF, but RIF is seldom used against NTM and is excluded by

definition from MDR-TB regimens. Finally, TMC207 has shown cidal activity against *Mycobacterium leprae* in mice at low dose, suggesting that it holds promise for leprosy patients (207).

E. Gaps in our understanding of the factors driving cure of TB disease— Since the early days of anti-TB therapy, the presence and extent of cavitary disease have often been cited as a predictor of poor clinical outcome, development of resistance and relapse (7, 208–210). There's likely to be a combination of reasons behind the difficulty to sterilize cavities. The number of bacilli is highest in these lesions due to permissive growth conditions either extracellularly or inside resting macrophages, providing a huge reservoir for the acquisition of spontaneous resistance mutations (124). The diversity of microenvironments and microbial subpopulations in cavities may be higher than generally recognized, contrary to the commonly accepted dogma that most bacilli are extracellular and rapidly dividing in the presence of high oxygen tension. Persister-like bacilli containing lipid bodies, tolerant to the cidal action of antibiotics, were consistently found in sputum, along with actively replicating bacteria (211, 212). Finally, penetration of chemotherapeutic agents may be hindered by thick fibrotic cavity walls. To develop new drugs and optimize the use of existing drugs for sterilizing cavities, we need to improve our understanding of the dynamic of cavity resolution in response to individual drugs, and the extent of penetration of these drugs in the different cavitary subcompartments. Modern technologies, such as PET imaging and scanning mass spectrometry of resected lesions in animal models and patients, are a potential way forward. In parallel, the predictive value of available biomarkers to evaluate cavity resolution, such as EBA, drug concentrations in sputum and the whole blood bactericidal assay (213), should be investigated in standardized studies, both in the non-human primate model and in patient cohorts.

To a large extent, doses of second- and third-line TB drugs, which have been adopted in clinical trials and by TB clinicians, are those previously approved for labeled disease indications. Although TB is among the most complex infectious diseases, little has been invested in TB-specific proof-of-concept studies to optimize doses and dosing regimens using human pharmacological data. As a starting point, a systematic analysis of all available clinical and pharmacological data remains to be conducted to revisit second- and third-line drug doses in pulmonary TB. As shown recently (214), RIF may have been under-dosed for more than 40 years.

For most antibiotic classes used to treat acute infectious diseases, one defined PK/PD index has been shown to drive efficacy. These are either C_{max}/MIC (ratio between peak serum level and MIC), AUC/MIC (ratio between systemic exposure over the dosing interval and MIC) or T>MIC (percentage of the dosing interval during which plasma levels remain above the MIC). In the case of TB, a set of data is available for the FQs in the mouse model (165), where it is shown that AUC/MIC is the best predictor of overall bacterial load reduction in the lungs. But since TB is such a complex and chronic disease with varying levels of pathogen sequestration, combined with multiple metabolic states and cellular location of the bacilli, it is possible that different PK/PD indices drive the eradication of these different populations. Care should be taken when extrapolating results from animal PK/PD studies to humans, particularly when these are obtained from mice that present little of the typical

pathology of humans. An interesting approach was recently adopted to predict sterilizing doses of PZA, using a PK/PD model where human PK profile is simulated in an *in vitro* system that exclusively contains slowly replicating bacilli (215). Based on the results, sterilizing effect was driven by the AUC/MIC ratio, while resistance suppression correlated best with T>MIC. Monte Carlo simulations further indicated that currently recommended PZA doses (1.5 to 2g daily) would achieve sterilization in only 15 to 50% of the patients, based on actual drug levels observed in ELF. Classically, PK/PD indices are calculated using drug levels measured in plasma, sometimes corrected for protein binding, yet plasma is not the site of drug action in pulmonary TB. There is an urgent need for systematic studies of drug penetration in lesions such that more relevant PK/PD indices can be calculated and predictive PK/PD models can be built. These should include microdialysis to measure free drug levels at the site of infection, as protein binding in lesions and other infection sites is totally unknown.

Novel Delivery Systems to Increase Drug Levels in the Lungs

In parallel with the development of new drugs for TB, increasing efforts aim at reformulating existing and approved drugs to improve their therapeutic window and efficacy by increasing exposure at the site of infection while decreasing systemic drug levels. Inhalation therapy holds promise as an alternative route of administration that limits systemic side effects and delivers high, localized drug concentrations to the site of action (216). The best characterized system is probably inhaled tobramycin (TOBI®) developed for the treatment of lung infections in cystic fibrosis patients, where mean sputum concentrations are around 1000-fold higher than peak serum concentrations (217). This translates into a significant improvement in therapeutic ratio over that of parenteral AGs. A small clinical study with adjunctive aerosol AGs was conducted in pulmonary TB patients with persistent smear and culture positive sputum despite adequate treatment. Though this was not designed as a placebo controlled clinical trial, 68% of the subjects converted to smear negativity within 1–2 months (177).

There are several caveats and complications associated with the development and use of nebulizers. Only a fraction (1–20%) of the drug is deposited deep in the lung alveoli, while most of the drug placed in the nebulizer is wasted. The efficiency of deposition depends on the type of nebulizer (218), antibiotic solution (219), patient technique (220) and particle size. Particle size range is critical - typically the respirable range is 0.5 to 5.0 μm because particles < 0.5 μm are primarily exhaled whereas particles > 5.0 μm are trapped in the oropharynx (221). Development of an approved formulation compatible with this route of administration is key to avoid irritation, inflammation and hyper-sensitivity reactions. This adds to drug and device development costs, an issue which cannot be ignored when dealing with neglected diseases in developing countries. Finally, patients need to be educated with regard to the use, cleaning and maintenance of the nebulizer to avoid contamination problems and ensure optimal results.

Nevertheless, for some second- and third-line drugs with narrow therapeutic windows, inhalation may be the only strategy to achieve effective sputum and cavity concentrations while maintaining low systemic drug levels and associated toxicities. Despite all of these

complexities, nebulized inhalation therapy remains an exciting strategy to minimize systemic exposure and may constitute a preferred option over i.v. or i.m. injections of AGs or CAP.

A more robust and possibly more suitable solution for field use is the development of dry powder formulations, which benefit from reduced cost and complexity when compared to nebulization systems (222). These have been tested in animal models with CAP (223), PAS (224), INH and RBT (225). Overall, these studies have shown it is possible to achieve high ratios of lung fluid to plasma levels, increased duration of action due to sustained release, high volume of distribution, and high intracellular:extracellular ratio, though the mechanism of intracellular drug delivery was not elucidated.

Other systems based on liposomes, microparticles and nanoparticles administered either via inhalation (226) or intravenously (227) have been tested in animal studies, though none of them has reached the stage of clinical development (228). Again, the ultimate objective is to maximize efficacy and therapeutic index of existing TB drugs by exploring new technologies that improve bioavailability, increase concentrations at the site of action while decreasing blood levels and side effects.

As summarized in the previous section and Table 4, drug distribution in sequestered infection sites may be problematic for some drug classes, and in some lesion types. There is a need for systematic investigation of drug penetration not only in bronchial secretions, but also deep inside closed necrotic lesions and cavities. Identification of poor ‘penetrators’ may provide sufficient evidence to support the development of new formulation and devices for inhalation of TB drugs that do not penetrate infected tissues effectively via conventional routes. Thorough pre-clinical and clinical pharmacokinetic studies, including drug quantification in most if not all sites of infection, should be conducted to validate the development and use of aerosolized drugs against pulmonary TB in the clinic. Though several key issues need to be addressed before inhaled therapy finds its way from theory to clinical reality, the urgent need for more effective second- and third-line drugs justifies the investment, particularly since existing TB drugs are relatively inexpensive.

CONCLUSION

The term “polypharmacy” could have been literally invented to describe the chemotherapy of drug-resistant TB, yet in contrast to psychiatry and cardiology, two other disease areas with significant complexities in management introduced by co-administration of multiple medicines, there are relatively few studies that either provide baseline PK/PD information or systematically evaluate DDI in the second- and third-line agents used to treat patients suffering from MDR disease. As a consequence of this, TDM is virtually completely absent from the medical lexicon of most physicians involved in MDR-TB management. We understand the PK of most of the existing drugs and their potency *in vitro*, and these data are comprehensively compiled in this review for the first time. Yet there is no clear relationship between *in vitro* potency and *in vivo* efficacy and therefore no way of relating these PK/PD data directly to the outcome of patients on such regimens. To optimize the benefit of TDM - a reliable and accurate tool for pharmacokinetic assessment - and justify its additional cost,

predictive pharmacodynamic read-outs and lesion-to-plasma drug level ratios remain to be established or improved.

EBA for many of these agents has been done, but while relatively inexpensive and straightforward, it does not appear to correlate with either *in vitro* efficacy nor demonstrated clinical utility for achieving ultimate cure (consider the dramatically higher EBA for INH vs. RIF compared to the much greater impact of RIF on sterilizing durable cure as one obvious example). There are, of course, the occasional agents (like the FQs) that are so potent and so well-studied for other diseases, and for which clinical efficacy is clearly demonstrated. But the recent realization that RIF levels are sub-optimal in many patients highlights that even for first-line agents these aspects are understudied. The recent emergence of new imaging methodologies, coupled to EBA-like short term monotherapy methodology, might provide the bridging clinical information necessary to translate drug levels into efficacy by revealing information on lesion-specific responses to various agents. But a dramatic increase in focus and intensity of such studies is urgently needed to combat the rising tide of MDR and XDR disease.

Agents currently in clinical development, namely TMC207, offer the potential for radically changing the landscape in exciting new ways. But since these are not informed by detailed knowledge of what the limitations of current agents actually are, the chance of identifying a new agent with an improved profile in sterilizing activity that would dramatically shorten the course of therapy are really no better than they were in the 1950s. Since the expense of developing a single new agent greatly exceed the combined expenses of detailed PK/PD studies of the kind described here there is a strong economic argument to be made for aggressively pursuing such information. These kinds of detailed studies, whether they result in dosing adjustment, alterations in delivery strategies, or just a deeper understanding of what physicochemical parameters correlate with tissue penetration to the site of disease, are urgently needed and largely neglected.

ACKNOWLEDGEMENTS

We would like to gratefully acknowledge Thomas Dick (NITD), Matthew Carroll (NIH), Doosoo Jeon (National Masan Tuberculosis Hospital, Masan, South Korea), Helena Boshoff (NIH) and Laura Via (NIH) for unpublished information and helpful discussions. Inhee Choi (NIH) provided assistance with calculation of cLogP for existing agents and Jason LeBlanc with preparing the manuscript. We are grateful to Thomas Parr Jr. (The Medicine Company) and Denis Mitchison for stimulating discussions on early clinical data and antibiotic principles. This research was supported in part by the Intramural Research Program of the National Institutes of Health.

ABBREVIATIONS

AG	Aminoglycoside
AM	Alveolar Macrophage
AMI	Amikacin
AUC	Area Under the Concentration-Time Curve
CAP	Capreomycin

CLA	Clarithromycin
CLO	Clofazimine
C_{max}	Peak plasma concentration
CS	Cycloserine
DDI	Drug-Drug Interactions
DST	Drug Susceptibility Testing
EBA	Early Bactericidal Activity
ELF	Epithelium Lining Fluid
EMB	Ethambutol
ETH	Ethionamide
FQ	Fluoroquinolone
INH	Isoniazid
KAN	Kanamycin
LEV	Levofloxacin
LZD	Linezolid
MBC	Minimum Bactericidal Concentration
MDR	Multi-Drug Resistant
MIC	Minimum Inhibitory Concentration
MPC	Mutant Prevention Concentration
Mtb	*Mycobacterium tuberculosis*
MTZ	Metronidazole
MXF	Moxifloxacin
OFX	Ofloxacin
PAS	Para-Amino-Salicylate
PD	Pharmacodynamics
PK	Pharmacokinetics
PTH	Prothionamide
PZA	Pyrazinamide
RBT	Rifabutin

RIF	Rifampicin
STR	Streptomycin
TDM	Therapeutic Drug Monitoring
T_{max}	Time of Peak Plasma Concentration
V_{ss}	Volume of Distribution at Steady State
XDR	Extensively Drug Resistant

REFERENCES

1. Bass JB, Jr., Farer LS, Hopewell PC, et al. Treatment of tuberculosis and tuberculosis infection in adults and children. American Thoracic Society and The Centers for Disease Control and Prevention. Am J Respir Crit Care Med. 1994; 149: 1359–74. [PubMed: 8173779]
2. Iseman MD. Treatment of multidrug-resistant tuberculosis. N Engl J Med. 1993; 329: 784–91. [PubMed: 8350889]
3. Chan ED, Iseman MD. Multidrug-resistant and extensively drug-resistant tuberculosis: a review. Curr Opin Infect Dis. 2008; 21: 587–95. [PubMed: 18978526]
4. Bonilla CA, Crossa A, Jave HO, et al. Management of extensively drug-resistant tuberculosis in Peru: cure is possible. PLoS ONE. 2008; 3: e2957. [PubMed: 18698423]
5. Mitnick CD, Shin SS, Seung KJ, et al. Comprehensive treatment of extensively drug-resistant tuberculosis. N Engl J Med. 2008; 359: 563–74. [PubMed: 18687637]
6. Migliori GB, Lange C, Centis R, et al. Resistance to second-line injectables and treatment outcomes in multidrug-resistant and extensively drug-resistant tuberculosis cases. Eur Respir J. 2008; 31: 1155–9. [PubMed: 18515555]
7. Kim DH, Kim HJ, Park SK, et al. Treatment outcomes and long-term survival in patients with extensively drug-resistant tuberculosis. Am J Respir Crit Care Med. 2008; 178: 1075–82. [PubMed: 18703792]
8. Kwon YS, Kim YH, Suh GY, et al. Treatment outcomes for HIV-uninfected patients with multidrug-resistant and extensively drug-resistant tuberculosis. Clin Infect Dis. 2008; 47: 496–502. [PubMed: 18611154]
9. Jeon CY, Hwang SH, Min JH, et al. Extensively drug-resistant tuberculosis in South Korea: risk factors and treatment outcomes among patients at a tertiary referral hospital. Clin Infect Dis. 2008; 46: 42–9. [PubMed: 18171212]
10. Gandhi NR, Moll A, Sturm AW, et al. Extensively drug-resistant tuberculosis as a cause of death in patients co-infected with tuberculosis and HIV in a rural area of South Africa.Lancet. 2006; 368: 1575–80. [PubMed: 17084757]
11. Chan ED, Strand MJ, Iseman MD. Treatment outcomes in extensively resistant tuberculosis. N Engl J Med. 2008; 359: 657–9.
12. Coyne KM, Pozniak AL, Lamorde M, Boffito M. Pharmacology of second-line antituberculosis drugs and potential for interactions with antiretroviral agents. Aids. 2009; 23: 437–46. [PubMed: 19256042]
13. Peloquin CA. Pharmacological issues in the treatment of tuberculosis. Ann N Y Acad Sci. 2001; 953: 157–64. [PubMed: 11795409]
14. McGuigan M Antituberculosis Drugs In: Dart R, editor. Medical Toxicology. 3rd Edition ed: Lippincott, WIlliams & Wilkins; 2004; p. 434–43.
15. Drug resistant Tuberculosis: A Survival Guide for Clinicians; 2004.
16. Handbook of Anti-Tuberculosis Agents: Elsevier; 2008.
17. WHO. Treatment of Tuberculosis: Guidelines for National Programmes. 3rd Edition ed; 2003 p. 57–60.
18. Treatment of Tuberculosis. Atlanta: CDC; 2003 6 20,

19. Park SK, Lee WC, Lee DH, et al. Self-administered, standardized regimens for multidrug-resistant tuberculosis in South Korea. Int J Tuberc Lung Dis. 2004; 8: 361–8. [PubMed: 15139476]
20. Tabarsi P, Baghaei P, Jalali S, et al. Is standardized treatment appropriate for non-XDR multiple drug resistant tuberculosis cases? A clinical descriptive study. Scand J Infect Dis. 2009; 41: 10–3. [PubMed: 19037820]
21. Balabanova Y, Ruddy M, Hubb J, et al. Multidrug-resistant tuberculosis in Russia: clinical characteristics, analysis of second-line drug resistance and development of standardized therapy. Eur J Clin Microbiol Infect Dis. 2005; 24: 136–9. [PubMed: 15666160]
22. Mak A, Thomas A, Del Granado M, et al. Influence of multidrug resistance on tuberculosis treatment outcomes with standardized regimens. Am J Respir Crit Care Med. 2008; 178: 306–12. [PubMed: 18511706]
23. Timperi R, Han LL, Sloutsky A, et al. Drug resistance profiles of Mycobacterium tuberculosis isolates: five years' experience and insight into treatment strategies for MDR-TB in Lima, Peru. Int J Tuberc Lung Dis. 2005; 9: 175–80. [PubMed: 15732737]
24. Saravia JC, Appleton SC, Rich ML, et al. Retreatment management strategies when first-line tuberculosis therapy fails. Int J Tuberc Lung Dis. 2005; 9: 421–9. [PubMed: 15830748]
25. Mitrzyk BM. Treatment of extensively drug-resistant tuberculosis and role of the pharmacist. Pharmacotherapy. 2008; 28: 1243–54. [PubMed: 18823220]
26. Wells CD, Cegielski JP, Nelson LJ, et al. HIV infection and multidrug-resistant tuberculosis: the perfect storm. J Infect Dis. 2007; 196 Suppl 1: S86–107. [PubMed: 17624830]
27. Senol G, Erbaycu A, Ozsoz A. Incidence of cross resistance between rifampicin and rifabutin in Mycobacterium tuberculosis strains in Izmir, Turkey. J Chemother. 2005; 17: 380–4. [PubMed: 16167516]
28. Chien HP, Yu MC, Ong TF, Lin TP, Luh KT. In vitro activity of rifabutin and rifampin against clinical isolates of Mycobacterium tuberculosis in Taiwan. J Formos Med Assoc. 2000; 99: 408–11. [PubMed: 10870331]
29. Sintchenko V, Chew WK, Jelfs PJ, Gilbert GL. Mutations in rpoB gene and rifabutin susceptibility of multidrug-resistant Mycobacterium tuberculosis strains isolated in Australia. Pathology. 1999; 31: 257–60. [PubMed: 10503273]
30. Hugonnet JE, Tremblay LW, Boshoff HI, Barry CE, 3rd, Blanchard JS. Meropenem clavulanate is effective against extensively drug-resistant Mycobacterium tuberculosis. Science. 2009; 323: 1215–8. [PubMed: 19251630]
31. van den Boogaard J, Kibiki GS, Kisanga ER, Boeree MJ, Aarnoutse RE. New drugs against tuberculosis: problems, progress, and evaluation of agents in clinical development. Antimicrob Agents Chemother. 2009; 53: 849–62. [PubMed: 19075046]
32. Rivers EC, Mancera RL. New anti-tuberculosis drugs with novel mechanisms of action. Curr Med Chem. 2008; 15: 1956–67. [PubMed: 18691051]
33. Yew WW, Cheung SW, Chau CH, et al. Serum pharmacokinetics of antimycobacterial drugs in patients with multidrug-resistant tuberculosis during therapy. Int J Clin Pharmacol Res. 1999; 19: 65–71. [PubMed: 10761535]
34. Barroso EC, Pinheiro VG, Facanha MC, et al. Serum concentrations of rifampin, isoniazid, and intestinal absorption, permeability in patients with multidrug resistant tuberculosis. Am J Trop Med Hyg. 2009; 81: 322–9. [PubMed: 19635892]
35. Burman WJ, Gallicano K, Peloquin C. Comparative pharmacokinetics and pharmacodynamics of the rifamycin antibacterials. Clin Pharmacokinet. 2001; 40: 327–41. [PubMed: 11432536]
36. Narang PK, Lewis RC, Bianchine JR. Rifabutin absorption in humans: relative bioavailability and food effect. Clin Pharmacol Ther. 1992; 52: 335–41. [PubMed: 1330396]
37. Nijland HM, Ruslami R, Stalenhoef JE, et al. Exposure to rifampicin is strongly reduced in patients with tuberculosis and type 2 diabetes. Clin Infect Dis. 2006; 43: 848–54. [PubMed: 16941365]
38. Peloquin CA, Nitta AT, Burman WJ, et al. Low antituberculosis drug concentrations in patients with AIDS. Ann Pharmacother. 1996; 30: 919–25. [PubMed: 8876848]
39. Gilljam M, Berning SE, Peloquin CA, Strandvik B, Larsson LO. Therapeutic drug monitoring in patients with cystic fibrosis and mycobacterial disease. Eur Respir J. 1999; 14: 347–51. [PubMed: 10515412]

40. Weiner M, Benator D, Burman W, et al. Association between acquired rifamycin resistance and the pharmacokinetics of rifabutin and isoniazid among patients with HIV and tuberculosis. Clin Infect Dis. 2005; 40: 1481–91. [PubMed: 15844071]
41. Hafner R, Bethel J, Power M, et al. Tolerance and pharmacokinetic interactions of rifabutin and clarithromycin in human immunodeficiency virus-infected volunteers. Antimicrob Agents Chemother. 1998; 42: 631–9. [PubMed: 9517944]
42. Berning SE, Peloquin CA. Antimicrobial agents: para-aminosalicylic acid In: Yu VL, Merigan TC, Barriere S, White NJ, editors. Antimicrobial Chemotherapy and Vaccines. Baltimore, MD: Williams and Wilkins; 1998; p. 663–8.
43. Skinner MH, Blaschke TF. Clinical pharmacokinetics of rifabutin. Clin Pharmacokinet. 1995; 28: 115–25. [PubMed: 7736687]
44. Peloquin CA, Hadad DJ, Molino LP, et al. Population pharmacokinetics of levofloxacin, gatifloxacin, and moxifloxacin in adults with pulmonary tuberculosis. Antimicrob Agents Chemother. 2008; 52: 852–7. [PubMed: 18070980]
45. Lubasch A, Keller I, Borner K, Koeppe P, Lode H. Comparative pharmacokinetics of ciprofloxacin, gatifloxacin, grepafloxacin, levofloxacin, trovafloxacin, and moxifloxacin after single oral administration in healthy volunteers. Antimicrob Agents Chemother. 2000; 44: 2600–3. [PubMed: 10991830]
46. Webb DB, Roberts DE, Williams JD, Asscher AW. Pharmacokinetics of ciprofloxacin in healthy volunteers and patients with impaired kidney function. J Antimicrob Chemother. 1986; 18 Suppl D: 83–7.
47. Stass H, Kubitza D. Pharmacokinetics and elimination of moxifloxacin after oral and intravenous administration in man. J Antimicrob Chemother. 1999; 43 Suppl B: 83–90.
48. Zhu M, Burman WJ, Jaresko GS, et al. Population pharmacokinetics of intravenous and intramuscular streptomycin in patients with tuberculosis. Pharmacotherapy. 2001; 21: 1037–45. [PubMed: 11560193]
49. Holdiness MR. Clinical pharmacokinetics of the antituberculosis drugs. Clin Pharmacokinet. 1984; 9: 511–44. [PubMed: 6391781]
50. Tod M, Lortholary O, Seytre D, et al. Population pharmacokinetic study of amikacin administered once or twice daily to febrile, severely neutropenic adults. Antimicrob Agents Chemother. 1998; 42: 849–56. [PubMed: 9559795]
51. Zhu M, Starke JR, Burman WJ, et al. Population pharmacokinetic modeling of pyrazinamide in children and adults with tuberculosis. Pharmacotherapy. 2002; 22: 686–95. [PubMed: 12066959]
52. Peloquin CA, Zhu M, Adam RD, Singleton MD, Nix DE. Pharmacokinetics of para-aminosalicylic acid granules under four dosing conditions. Ann Pharmacother. 2001; 35: 1332–8. [PubMed: 11724078]
53. Zhu M, Nix DE, Adam RD, Childs JM, Peloquin CA. Pharmacokinetics of cycloserine under fasting conditions and with high-fat meal, orange juice, and antacids. Pharmacotherapy. 2001; 21: 891–7. [PubMed: 11718495]
54. Peloquin CA, Auclair B. Pharmacology of the second-line antituberculosis drugs In: Bastian I, Portaels F, editors. Multidrug-Resistant Tuberculosis. Netherlands: Kluwer Academic Publishers; 2000; p. 163–74.
55. Zhu M, Namdar R, Stambaugh JJ, et al. Population pharmacokinetics of ethionamide in patients with tuberculosis. Tuberculosis (Edinb). 2002; 82: 91–6. [PubMed: 12356460]
56. Auclair B, Nix DE, Adam RD, James GT, Peloquin CA. Pharmacokinetics of ethionamide administered under fasting conditions or with orange juice, food, or antacids. Antimicrob Agents Chemother. 2001; 45: 810–4. [PubMed: 11181366]
57. Rodvold KA. Clinical pharmacokinetics of clarithromycin. Clin Pharmacokinet. 1999; 37: 385–98. [PubMed: 10589373]
58. Brogden RN, Carmine A, Heel RC, et al. Amoxycillin/clavulanic acid: a review of its antibacterial activity, pharmacokinetics and therapeutic use. Drugs. 1981; 22: 337–62. [PubMed: 7037354]
59. Slatter JG, Stalker DJ, Feenstra KL, et al. Pharmacokinetics, metabolism, and excretion of linezolid following an oral dose of [^{14}C]linezolid to healthy human subjects. Drug Metab Dispos. 2001; 29: 1136–45. [PubMed: 11454733]

60. Meagher AK, Forrest A, Rayner CR, Birmingham MC, Schentag JJ. Population pharmacokinetics of linezolid in patients treated in a compassionate-use program. Antimicrob Agents Chemother. 2003; 47: 548–53. [PubMed: 12543657]

61. Nix DE, Adam RD, Auclair B, et al. Pharmacokinetics and relative bioavailability of clofazimine in relation to food, orange juice and antacid. Tuberculosis (Edinb). 2004; 84: 365–73. [PubMed: 15525560]

62. Sprandel KA, Schriever CA, Pendland SL, et al. Pharmacokinetics and pharmacodynamics of intravenous levofloxacin at 750 milligrams and various doses of metronidazole in healthy adult subjects. Antimicrob Agents Chemother. 2004; 48: 4597–605. [PubMed: 15561831]

63. Houghton GW, Thorne PS, Smith J, Templeton R, Collier J. Comparison of the pharmacokinetics of metronidazole in healthy female volunteers following either a single oral or intravenous dose. Br J Clin Pharmacol. 1979; 8: 337–41. [PubMed: 508508]

64. Rustomjee R, Diacon AH, Allen J, et al. Early bactericidal activity and pharmacokinetics of the diarylquinoline TMC207 in treatment of pulmonary tuberculosis. Antimicrob Agents Chemother. 2008; 52: 2831–5. [PubMed: 18505852]

65. Diacon AH, Pym A, Grobusch M, et al. The diarylquinoline TMC207 for multidrug-resistant tuberculosis. N Engl J Med. 2009; 360: 2397–405. [PubMed: 19494215]

66. Peloquin CA. Therapeutic drug monitoring of the antimycobacterial drugs. Clin Lab Med. 1996; 16: 717–29. [PubMed: 8866188]

67. Peloquin CA. Therapeutic drug monitoring in the treatment of tuberculosis. Drugs. 2002; 62: 2169–83. [PubMed: 12381217]

68. Li J, Burzynski JN, Lee YA, et al. Use of therapeutic drug monitoring for multidrug-resistant tuberculosis patients. Chest. 2004; 126: 1770–6. [PubMed: 15596672]

69. German N, Malik M, Rosen JD, Drlica K, Kerns RJ. Use of gyrase resistance mutants to guide selection of 8-methoxy-quinazoline-2,4-diones. Antimicrob Agents Chemother. 2008; 52: 3915–21. [PubMed: 18765690]

70. Perlman DC, Segal Y, Rosenkranz S, et al. The clinical pharmacokinetics of rifampin and ethambutol in HIV-infected persons with tuberculosis. Clin Infect Dis. 2005; 41: 1638–47. [PubMed: 16267738]

71. Schaaf HS, Willemse M, Cilliers K, et al. Rifampin pharmacokinetics in children, with and without human immunodeficiency virus infection, hospitalized for the management of severe forms of tuberculosis. BMC Med. 2009; 7: 19. [PubMed: 19386087]

72. Holland DP, Hamilton CD, Weintrob AC, et al. Therapeutic drug monitoring of antimycobacterial drugs in patients with both tuberculosis and advanced human immunodeficiency virus infection. Pharmacotherapy. 2009; 29: 503–10. [PubMed: 19397460]

73. Peloquin CA. Using therapeutic drug monitoring to dose the antimycobacterial drugs. Clin Chest Med. 1997; 18: 79–87. [PubMed: 9098612]

74. Schumacher GE, Barr JT. Total testing process applied to therapeutic drug monitoring: impact on patients' outcomes and economics. Clin Chem. 1998; 44: 370–4. [PubMed: 9474047]

75. Schumacher GE, Barr JT. Therapeutic drug monitoring: do the improved outcomes justify the costs? Clin Pharmacokinet. 2001; 40: 405–9. [PubMed: 11475466]

76. Goutelle S, Bourguignon L, Maire PH, et al. Pharmacokinetics and Antituberculosis Pharmacodynamics of Rifampin in Lungs: a Population Modeling and Monte Carlo Simulation Study. Antimicrob Agents Chemother. 2009.

77. Rastogi N, Labrousse V, Goh KS. In vitro activities of fourteen antimicrobial agents against drug susceptible and resistant clinical isolates of Mycobacterium tuberculosis and comparative intracellular activities against the virulent H37Rv strain in human macrophages. Curr Microbiol. 1996; 33: 167–75. [PubMed: 8672093]

78. Lee CN, Heifets LB. Determination of minimal inhibitory concentrations of antituberculosis drugs by radiometric and conventional methods. Am Rev Respir Dis. 1987; 136: 349–52. [PubMed: 3619193]

79. Warren RM, Streicher EM, Gey van Pittius NC, et al. The clinical relevance of Mycobacterial pharmacogenetics. Tuberculosis (Edinb). 2009.

80. Bryant RE, Fox K, Oh G, Morthland VH. Beta-lactam enhancement of aminoglycoside activity under conditions of reduced pH and oxygen tension that may exist in infected tissues. J Infect Dis. 1992; 165: 676–82. [PubMed: 1552196]
81. Baciewicz AM, Chrisman CR, Finch CK, Self TH. Update on rifampin and rifabutin drug interactions. Am J Med Sci. 2008; 335: 126–36. [PubMed: 18277121]
82. Baciewicz AM, Self TH. Rifampin drug interactions. Arch Intern Med. 1984; 144: 1667–71. [PubMed: 6380442]
83. Finch CK, Chrisman CR, Baciewicz AM, Self TH. Rifampin and rifabutin drug interactions: an update. Arch Intern Med. 2002; 162: 985–92. [PubMed: 11996607]
84. Nijland HM, Ruslami R, Suroto AJ, et al. Rifampicin reduces plasma concentrations of moxifloxacin in patients with tuberculosis. Clin Infect Dis. 2007; 45: 1001–7. [PubMed: 17879915]
85. Weiner M, Burman W, Luo CC, et al. Effects of rifampin and multidrug resistance gene polymorphism on concentrations of moxifloxacin. Antimicrob Agents Chemother. 2007; 51: 2861–6. [PubMed: 17517835]
86. Stass H, Kubitza D. Profile of moxifloxacin drug interactions. Clin Infect Dis. 2001; 32 Suppl 1: S47–50. [PubMed: 11249829]
87. Cheng KL, Nafziger AN, Peloquin CA, Amsden GW. Effect of grapefruit juice on clarithromycin pharmacokinetics. Antimicrob Agents Chemother. 1998; 42: 927–9. [PubMed: 9559810]
88. Roedler R, Neuhauser MM, Penzak SR. Does metronidazole interact with CYP3A substrates by inhibiting their metabolism through this metabolic pathway? Or should other mechanisms be considered? Ann Pharmacother. 2007; 41: 653–8. [PubMed: 17374625]
89. Lounis N, Gevers T, Van Den Berg J, Andries K. Impact of the interaction of R207910 with rifampin on the treatment of tuberculosis studied in the mouse model. Antimicrob Agents Chemother. 2008; 52: 3568–72. [PubMed: 18644960]
90. Benedetti MS. Inducing properties of rifabutin, and effects on the pharmacokinetics and metabolism of concomitant drugs. Pharmacol Res. 1995; 32: 177–87. [PubMed: 8866833]
91. Boulanger C, Hollender E, Farrell K, et al. Pharmacokinetic evaluation of rifabutin in combination with lopinavir-ritonavir in patients with HIV infection and active tuberculosis. Clin Infect Dis. 2009; 49: 1305–11. [PubMed: 19807276]
92. Zhaoxu L, Jingcheng T, Jinnan Z. Rifabutin autoinduction is caused by involvement of cytochrome P450 and cholinesterase. Pharmazie. 2008; 63: 156–9. [PubMed: 18380404]
93. Iatsimirskaia E, Tulebaev S, Storozhuk E, et al. Metabolism of rifabutin in human enterocyte and liver microsomes: kinetic parameters, identification of enzyme systems, and drug interactions with macrolides and antifungal agents. Clin Pharmacol Ther. 1997; 61: 554–62. [PubMed: 9164417]
94. Nishimura Y, Kurata N, Sakurai E, Yasuhara H. Inhibitory effect of antituberculosis drugs on human cytochrome P450-mediated activities. J Pharmacol Sci. 2004; 96: 293–300. [PubMed: 15528841]
95. Grange JM, Winstanley PA, Davies PD. Clinically significant drug interactions with antituberculosis agents. Drug Saf. 1994; 11: 242–51. [PubMed: 7848544]
96. Boman G Serum concentration and half-life of rifampicin after simultaneous oral administration of aminosalicylic acid or isoniazid. Eur J Clin Pharmacol. 1974; 7: 217–25. [PubMed: 4854257]
97. Tiitinen H Modification by para-aminosalicylic acid and sulfamethazine of the isoniazid inactivation in man. Scand J Respir Dis. 1969; 50: 281–90. [PubMed: 5380785]
98. Lehmann J The role of the metabolism of p-aminosalicylic acid (PAS) in the treatment of tuberculosis. Interaction with the metabolism of isonicotinic acid hydrazide (INH) and the synthesis of cholesterol. Scand J Respir Dis. 1969; 50: 169–85. [PubMed: 5195904]
99. O'Reilly RA. The stereoselective interaction of warfarin and metronidazole in man. N Engl J Med. 1976; 295: 354–7. [PubMed: 934223]
100. Muller M, dela Pena A, Derendorf H. Issues in pharmacokinetics and pharmacodynamics of anti-infective agents: distribution in tissue. Antimicrob Agents Chemother. 2004; 48: 1441–53. [PubMed: 15105091]

101. Sauermann R, Karch R, Langenberger H, et al. Antibiotic abscess penetration: fosfomycin levels measured in pus and simulated concentration-time profiles. Antimicrob Agents Chemother. 2005; 49: 4448–54. [PubMed: 16251282]
102. Wagner C, Sauermann R, Joukhadar C. Principles of antibiotic penetration into abscess fluid. Pharmacology. 2006; 78: 1–10. [PubMed: 16864973]
103. Bartlett JG. Experimental aspects of intraabdominal abscess. Am J Med. 1984; 76: 91–8.
104. Via LE, Lin PL, Ray SM, et al. Tuberculous Granulomas are Hypoxic in Guinea pigs, Rabbits, and Non-Human Primates. Infect Immun. 2008.
105. Carbon C, Cremieux AC, Fantin B. Pharmacokinetic and pharmacodynamic aspects of therapy of experimental endocarditis. Infect Dis Clin North Am. 1993; 7: 37–51. [PubMed: 8463652]
106. Cremieux AC, Maziere B, Vallois JM, et al. Ceftriaxone diffusion into cardiac fibrin vegetation. Qualitative and quantitative evaluation by autoradiography. Fundam Clin Pharmacol. 1991; 5: 53–60. [PubMed: 2066051]
107. Barclay WR, Ebert RH, Le Roy GV, Manthei RW, Roth LJ. Distribution and excretion of radioactive isoniazid in tuberculous patients. J Am Med Assoc. 1953; 151: 1384–8. [PubMed: 13034481]
108. Kislitsyna NA, Kotova NI. [Rifampicin and isoniazid concentration in the blood and resected lungs in tuberculosis with combined use of the preparations]. Probl Tuberk. 1980: 63–5.
109. Kislitsyna NA. [Comparative evaluation of rifampicin and isoniazid penetration into the pathological foci of the lungs in tuberculosis patients]. Probl Tuberk. 1985: 55–7.
110. Canetti G, Parrot R, Porven G, Le Lirzin M. [Rifomycin levels in the lung and tuberculous lesions in man]. Acta Tuberc Pneumol Belg. 1969; 60: 315–22. [PubMed: 5371667]
111. Kiss IJ, Farago E, Juhaz I, Bacsa S, Fabian E. Investigation on the serum and lung tissue level of rifampicin in man. Int J Clin Pharmacol Biopharm. 1976; 13: 42–7. [PubMed: 1248917]
112. Baldwin DR, Honeybourne D, Wise R. Pulmonary disposition of antimicrobial agents: methodological considerations. Antimicrob Agents Chemother. 1992; 36: 1171–5. [PubMed: 1416816]
113. Kiem S, Schentag JJ. Interpretation of antibiotic concentration ratios measured in epithelial lining fluid. Antimicrob Agents Chemother. 2008; 52: 24–36. [PubMed: 17846133]
114. Scaglione F, Demartini G, Dugnani S, Fraschini F. A new model examining intracellular and extracellular activity of amoxicillin, azithromycin, and clarithromycin in infected cells. Chemotherapy. 1993; 39: 416–23. [PubMed: 8222870]
115. Boselli E, Breilh D, Djabarouti S, et al. Reliability of mini-bronchoalveolar lavage for the measurement of epithelial lining fluid concentrations of tobramycin in critically ill patients. Intensive Care Med. 2007; 33: 1519–23. [PubMed: 17530217]
116. Moriarty TF, McElnay JC, Elborn JS, Tunney MM. Sputum antibiotic concentrations: implications for treatment of cystic fibrosis lung infection. Pediatr Pulmonol. 2007; 42: 1008–17. [PubMed: 17902147]
117. Mendelman PM, Smith AL, Levy J, et al. Aminoglycoside penetration, inactivation, and efficacy in cystic fibrosis sputum. Am Rev Respir Dis. 1985; 132: 761–5. [PubMed: 3931522]
118. Donald PR, Sirgel FA, Venter A, et al. The early bactericidal activity of amikacin in pulmonary tuberculosis. Int J Tuberc Lung Dis. 2001; 5: 533–8. [PubMed: 11409580]
119. Bergan T, Engeset A, Olszewski W. Does serum protein binding inhibit tissue penetration of antibiotics? Rev Infect Dis. 1987; 9: 713–8. [PubMed: 3326121]
120. Van de Velde S, Nguyen HA, Van Bambeke F, et al. Contrasting effects of human THP-1 cell differentiation on levofloxacin and moxifloxacin intracellular accumulation and activity against Staphylococcus aureus and Listeria monocytogenes. J Antimicrob Chemother. 2008; 62: 518–21. [PubMed: 18544595]
121. Zhang Y, Scorpio A, Nikaido H, Sun Z. Role of acid pH and deficient efflux of pyrazinoic acid in unique susceptibility of Mycobacterium tuberculosis to pyrazinamide. J Bacteriol. 1999; 181: 2044–9. [PubMed: 10094680]
122. Hanoulle X, Wieruszeski JM, Rousselot-Pailley P, et al. Selective intracellular accumulation of the major metabolite issued from the activation of the prodrug ethionamide in mycobacteria. J Antimicrob Chemother. 2006; 58: 768–72. [PubMed: 16895935]

123. Wang F, Langley R, Gulten G, et al. Mechanism of thioamide drug action against tuberculosis and leprosy. J Exp Med. 2007; 204: 73–8. [PubMed: 17227913]

124. Kaplan G, Post FA, Moreira AL, et al. Mycobacterium tuberculosis growth at the cavity surface: a microenvironment with failed immunity. Infect Immun. 2003; 71: 7099–108. [PubMed: 14638800]

125. Soman A, Honeybourne D, Andrews J, Jevons G, Wise R. Concentrations of moxifloxacin in serum and pulmonary compartments following a single 400 mg oral dose in patients undergoing fibre-optic bronchoscopy. J Antimicrob Chemother. 1999; 44: 835–8. [PubMed: 10590288]

126. Barcia-Macay M, Seral C, Mingeot-Leclercq MP, Tulkens PM, Van Bambeke F. Pharmacodynamic evaluation of the intracellular activities of antibiotics against Staphylococcus aureus in a model of THP-1 macrophages. Antimicrob Agents Chemother. 2006; 50: 841–51. [PubMed: 16495241]

127. Hutschala D, Skhirtladze K, Zuckermann A, et al. In vivo measurement of levofloxacin penetration into lung tissue after cardiac surgery. Antimicrob Agents Chemother. 2005; 49: 5107–11. [PubMed: 16304179]

128. Capitano B, Mattoes HM, Shore E, et al. Steady-state intrapulmonary concentrations of moxifloxacin, levofloxacin, and azithromycin in older adults. Chest. 2004; 125: 965–73. [PubMed: 15006955]

129. Conte JE, Jr., Golden JA, McQuitty M, et al. Effects of AIDS and gender on steady-state plasma and intrapulmonary ethionamide concentrations. Antimicrob Agents Chemother. 2000; 44: 1337–41. [PubMed: 10770772]

130. Conte JE, Jr., Golden JA, Duncan S, McKenna E, Zurlinden E. Intrapulmonary concentrations of pyrazinamide. Antimicrob Agents Chemother. 1999; 43: 1329–33. [PubMed: 10348747]

131. Acocella G, Carlone NA, Cuffini AM, Cavallo G. The penetration of rifampicin, pyrazinamide, and pyrazinoic acid into mouse macrophages. Am Rev Respir Dis. 1985; 132: 1268–73. [PubMed: 4073666]

132. Saralaya D, Peckham DG, Hulme B, et al. Serum and sputum concentrations following the oral administration of linezolid in adult patients with cystic fibrosis. J Antimicrob Chemother. 2004; 53: 325–8. [PubMed: 14729733]

133. Conte JE, Jr., Golden JA, Kipps J, Zurlinden E. Intrapulmonary pharmacokinetics of linezolid. Antimicrob Agents Chemother. 2002; 46: 1475–80. [PubMed: 11959585]

134. Fish DN, Gotfried MH, Danziger LH, Rodvold KA. Penetration of clarithromycin into lung tissues from patients undergoing lung resection. Antimicrob Agents Chemother. 1994; 38: 876–8. [PubMed: 8031063]

135. Rodvold KA, Gotfried MH, Danziger LH, Servi RJ. Intrapulmonary steady-state concentrations of clarithromycin and azithromycin in healthy adult volunteers. Antimicrob Agents Chemother. 1997; 41: 1399–402. [PubMed: 9174209]

136. Gould IM, Harvey G, Golder D, et al. Penetration of amoxycillin/clavulanic acid into bronchial mucosa with different dosing regimens. Thorax. 1994; 49: 999–1001. [PubMed: 7974318]

137. Cook PJ, Andrews JM, Woodcock J, Wise R, Honeybourne D. Concentration of amoxycillin and clavulanate in lung compartments in adults without pulmonary infection. Thorax. 1994; 49: 1134–8. [PubMed: 7831630]

138. Cox AL, Meewis JM, Horton R. Penetration into lung tissue after intravenous administration of amoxycillin/clavulanate. J Antimicrob Chemother. 1989; 24 Suppl B: 87–91.

139. Fraschini F, Scaglione F, Falchi M, et al. Pharmacokinetics and tissue distribution of amoxicillin plus clavulanic acid after oral administration in man. J Chemother. 1990; 2: 171–7. [PubMed: 2199627]

140. Weber DJ, Tolkoff-Rubin NE, Rubin RH. Amoxicillin and potassium clavulanate: an antibiotic combination. Mechanism of action, pharmacokinetics, antimicrobial spectrum, clinical efficacy and adverse effects. Pharmacotherapy. 1984; 4: 122–36. [PubMed: 6739312]

141. Cole PJ, Roberts DE, Davies SF, Knight RK. A simple oral antimicrobial regimen effective in severe chronic bronchial suppuration associated with culturable Haemophilus influenzae. J Antimicrob Chemother. 1983; 11: 109–13. [PubMed: 6601102]

142. Tulkens P, Trouet A. The uptake and intracellular accumulation of aminoglycoside antibiotics in lysosomes of cultured rat fibroblasts. Biochem Pharmacol. 1978; 27: 415–24. [PubMed: 24449]

143. Maurin M, Raoult D. Use of aminoglycosides in treatment of infections due to intracellular bacteria. Antimicrob Agents Chemother. 2001; 45: 2977–86. [PubMed: 11600345]

144. Traunmuller F, Zeitlinger M, Zeleny P, Muller M, Joukhadar C. Pharmacokinetics of single- and multiple-dose oral clarithromycin in soft tissues determined by microdialysis. Antimicrob Agents Chemother. 2007; 51: 3185–9. [PubMed: 17606673]

145. Mitchison DA. The action of antituberculosis drugs in short-course chemotherapy. Tubercle. 1985; 66: 219–25. [PubMed: 3931319]

146. Mitnick CD, Castro KG, Harrington M, Sacks LV, Burman W. Randomized trials to optimize treatment of multidrug-resistant tuberculosis. PLoS Med. 2007; 4: e292. [PubMed: 17988168]

147. Laserson KF, Thorpe LE, Leimane V, et al. Speaking the same language: treatment outcome definitions for multidrug-resistant tuberculosis. Int J Tuberc Lung Dis. 2005; 9: 640–5. [PubMed: 15971391]

148. Donald PR, Sirgel FA, Venter A, et al. Early bactericidal activity of antituberculosis agents. Expert Rev Anti Infect Ther. 2003; 1: 141–55. [PubMed: 15482107]

149. Sirgel FA, Botha FJ, Parkin DP, et al. The early bactericidal activity of rifabutin in patients with pulmonary tuberculosis measured by sputum viable counts: a new method of drug assessment. J Antimicrob Chemother. 1993; 32: 867–75. [PubMed: 8144427]

150. Chan SL, Yew WW, Ma WK, et al. The early bactericidal activity of rifabutin measured by sputum viable counts in Hong Kong patients with pulmonary tuberculosis. Tuber Lung Dis. 1992; 73: 33–8. [PubMed: 1326348]

151. Johnson JL, Hadad DJ, Boom WH, et al. Early and extended early bactericidal activity of levofloxacin, gatifloxacin and moxifloxacin in pulmonary tuberculosis. Int J Tuberc Lung Dis. 2006; 10: 605–12. [PubMed: 16776446]

152. Donald PR, Sirgel FA, Venter A, et al. The early bactericidal activity of streptomycin. Int J Tuberc Lung Dis. 2002; 6: 693–8. [PubMed: 12150481]

153. Jindani A, Dore CJ, Mitchison DA. Bactericidal and sterilizing activities of antituberculosis drugs during the first 14 days. Am J Respir Crit Care Med. 2003; 167: 1348–54. [PubMed: 12519740]

154. Botha FJ, Sirgel FA, Parkin DP, et al. Early bactericidal activity of ethambutol, pyrazinamide and the fixed combination of isoniazid, rifampicin and pyrazinamide (Rifater) in patients with pulmonary tuberculosis. S Afr Med J. 1996; 86: 155–8. [PubMed: 8619142]

155. Donald PR, Sirgel FA, Venter A, et al. Early bactericidal activity of amoxicillin in combination with clavulanic acid in patients with sputum smear-positive pulmonary tuberculosis. Scand J Infect Dis. 2001; 33: 466–9. [PubMed: 11450868]

156. Chambers HF, Kocagoz T, Sipit T, Turner J, Hopewell PC. Activity of amoxicillin/clavulanate in patients with tuberculosis. Clin Infect Dis. 1998; 26: 874–7. [PubMed: 9564467]

157. Dietze R, Hadad DJ, McGee B, et al. Early and extended early bactericidal activity of linezolid in pulmonary tuberculosis. Am J Respir Crit Care Med. 2008; 178: 1180–5. [PubMed: 18787216]

158. Garcia-Rodriguez JA, Gomez Garcia AC. In-vitro activities of quinolones against mycobacteria. J Antimicrob Chemother. 1993; 32: 797–808. [PubMed: 8144420]

159. Honeybourne D Antibiotic penetration in the respiratory tract and implications for the selection of antimicrobial therapy. Curr Opin Pulm Med. 1997; 3: 170–4. [PubMed: 9193864]

160. Gosling RD, Uiso LO, Sam NE, et al. The bactericidal activity of moxifloxacin in patients with pulmonary tuberculosis. Am J Respir Crit Care Med. 2003; 168: 1342–5. [PubMed: 12917230]

161. Burman WJ, Goldberg S, Johnson JL, et al. Moxifloxacin versus ethambutol in the first 2 months of treatment for pulmonary tuberculosis. Am J Respir Crit Care Med. 2006; 174: 331–8. [PubMed: 16675781]

162. Conde MB, Efron A, Loredo C, et al. Moxifloxacin versus ethambutol in the initial treatment of tuberculosis: a double-blind, randomised, controlled phase II trial. Lancet. 2009; 373: 1183–9. [PubMed: 19345831]

163. Rustomjee R, Lienhardt C, Kanyok T, et al. A Phase II study of the sterilising activities of ofloxacin, gatifloxacin and moxifloxacin in pulmonary tuberculosis. Int J Tuberc Lung Dis. 2008; 12: 128–38. [PubMed: 18230244]

164. Rodriguez JC, Cebrian L, Lopez M, et al. Mutant prevention concentration: comparison of fluoroquinolones and linezolid with Mycobacterium tuberculosis. J Antimicrob Chemother. 2004; 53: 441–4. [PubMed: 14963069]
165. Shandil RK, Jayaram R, Kaur P, et al. Moxifloxacin, ofloxacin, sparfloxacin, and ciprofloxacin against Mycobacterium tuberculosis: evaluation of in vitro and pharmacodynamic indices that best predict in vivo efficacy. Antimicrob Agents Chemother. 2007; 51: 576–82. [PubMed: 17145798]
166. Streptomycin treatment of pulmonary tuberculosis; 1948 10 30.
167. Crofton J, Mitchison DA. Streptomycin resistance in pulmonary tuberculosis. Br Med J. 1948; 2: 1009–15. [PubMed: 18100441]
168. Donald PR, Sirgel FA, Venter A, et al. The early bactericidal activity of a low-clearance liposomal amikacin in pulmonary tuberculosis. J Antimicrob Chemother. 2001; 48: 877–80. [PubMed: 11733472]
169. Hwang SS, Kim HR, Kim HJ, et al. Impact of resistance to first-line and injectable drugs on treatment outcomes in MDR-TB. Eur Respir J. 2009; 33: 581–5. [PubMed: 19251799]
170. Chan ED, Strand MJ, Iseman MD. Multidrug-resistant tuberculosis (TB) resistant to fluoroquinolones and streptomycin but susceptible to second-line injection therapy has a better prognosis than extensively drug-resistant TB. Clin Infect Dis. 2009; 48: e50–2. [PubMed: 19191632]
171. Maurin M, Raoult D. Phagolysosomal alkalinization and intracellular killing of Staphylococcus aureus by amikacin. J Infect Dis. 1994; 169: 330–6. [PubMed: 8106766]
172. McDermott W, Tompsett R. Activation of pyrazinamide and nicotinamide in acidic environments in vitro. Am Rev Tuberc. 1954; 70: 748–54. [PubMed: 13197751]
173. Converse PJ, Dannenberg AM, Jr., Estep JE, et al. Cavitary tuberculosis produced in rabbits by aerosolized virulent tubercle bacilli. Infect Immun. 1996; 64: 4776–87. [PubMed: 8890239]
174. Levy J, Smith AL, Kenny MA, Ramsey B, Schoenknecht FD. Bioactivity of gentamicin in purulent sputum from patients with cystic fibrosis or bronchiectasis: comparison with activity in serum. J Infect Dis. 1983; 148: 1069–76. [PubMed: 6418829]
175. Frimodt-Moller N How predictive is PK/PD for antibacterial agents? Int J Antimicrob Agents. 2002; 19: 333–9. [PubMed: 11978504]
176. Heifets L, Simon J, Pham V. Capreomycin is active against non-replicating M. tuberculosis. Ann Clin Microbiol Antimicrob. 2005; 4: 6. [PubMed: 15804353]
177. Sacks LV, Pendle S, Orlovic D, et al. Adjunctive salvage therapy with inhaled aminoglycosides for patients with persistent smear-positive pulmonary tuberculosis. Clin Infect Dis. 2001; 32: 44–9. [PubMed: 11118385]
178. Zhang Y, Permar S, Sun Z. Conditions that may affect the results of susceptibility testing of Mycobacterium tuberculosis to pyrazinamide. J Med Microbiol. 2002; 51: 42–9. [PubMed: 11800471]
179. Heifets L, Higgins M, Simon B. Pyrazinamide is not active against Mycobacterium tuberculosis residing in cultured human monocyte-derived macrophages. Int J Tuberc Lung Dis. 2000; 4: 491–5. [PubMed: 10864178]
180. Salfinger M, Crowle AJ, Reller LB. Pyrazinamide and pyrazinoic acid activity against tubercle bacilli in cultured human macrophages and in the BACTEC system. J Infect Dis. 1990; 162: 201–7. [PubMed: 2113074]
181. Crowle AJ, Sbarbaro JA, May MH. Inhibition by pyrazinamide of tubercle bacilli within cultured human macrophages. Am Rev Respir Dis. 1986; 134: 1052–5. [PubMed: 3535593]
182. Steele MA, Des Prez RM. The role of pyrazinamide in tuberculosis chemotherapy. Chest. 1988; 94: 845–50. [PubMed: 3048929]
183. Anonymous. Controlled trial of four thrice-weekly regimens and a daily regimen all given for 6 months for pulmonary tuberculosis. Lancet. 1981; 1: 171–4. [PubMed: 6109855]
184. Lew W, Pai M, Oxlade O, Martin D, Menzies D. Initial drug resistance and tuberculosis treatment outcomes: systematic review and meta-analysis. Ann Intern Med. 2008; 149: 123–34. [PubMed: 18626051]

185. Potter BP. A clinical appraisal of the value of para-aminosalicylic acid with and without streptomycin in the treatment of tuberculosis. Dis Chest. 1950; 17: 509–23. [PubMed: 15411858]

186. Lehmann J The treatment of tuberculosis in Sweden with para-aminosalicylic acid; a review. Dis Chest. 1949; 16: 684–703, [PubMed: 15396516]

187. Harbeck RJ, Worthen GS, Lebo TD, Peloquin CA. Clofazimine crystals in the cytoplasm of pulmonary macrophages. Ann Pharmacother. 1999; 33: 250. [PubMed: 10084424]

188. Forster DJ, Causey DM, Rao NA. Bull's eye retinopathy and clofazimine. Ann Intern Med. 1992; 116: 876–7.

189. Tomioka H Present status and future prospects of chemotherapeutics for intractable infections due to Mycobacterium avium complex. Curr Drug Discov Technol. 2004; 1: 255–68. [PubMed: 16472242]

190. Bhusal Y, Shiohira CM, Yamane N. Determination of in vitro synergy when three antimicrobial agents are combined against Mycobacterium tuberculosis. Int J Antimicrob Agents. 2005; 26: 292–7. [PubMed: 16150578]

191. Fortun J, Martin-Davila P, Navas E, et al. Linezolid for the treatment of multidrug-resistant tuberculosis. J Antimicrob Chemother. 2005; 56: 180–5. [PubMed: 15911549]

192. Wayne LG, Sramek HA. Metronidazole is bactericidal to dormant cells of Mycobacterium tuberculosis. Antimicrob Agents Chemother. 1994; 38: 2054–8. [PubMed: 7811018]

193. Cynamon MH, Palmer GS. In vitro activity of amoxicillin in combination with clavulanic acid against Mycobacterium tuberculosis. Antimicrob Agents Chemother. 1983; 24: 429–31. [PubMed: 6416162]

194. Schecter GF, Scott C, True L, et al. Linezolid in the Treatment of Multidrug-Resistant Tuberculosis. Clin Infect Dis. 2009.

195. Condos R, Hadgiangelis N, Leibert E, et al. Case series report of a linezolid-containing regimen for extensively drug-resistant tuberculosis. Chest. 2008; 134: 187–92. [PubMed: 18628223]

196. Yew WW, Chau CH, Wen KH. Linezolid in the treatment of 'difficult' multidrug-resistant tuberculosis. Int J Tuberc Lung Dis. 2008; 12: 345–6. [PubMed: 18284844]

197. Park IN, Hong SB, Oh YM, et al. Efficacy and tolerability of daily-half dose linezolid in patients with intractable multidrug-resistant tuberculosis. J Antimicrob Chemother. 2006; 58: 701–4. [PubMed: 16857689]

198. von der Lippe B, Sandven P, Brubakk O. Efficacy and safety of linezolid in multidrug resistant tuberculosis (MDR-TB)--a report of ten cases. J Infect. 2006; 52: 92–6. [PubMed: 15907341]

199. Chambers HF, Turner J, Schecter GF, Kawamura M, Hopewell PC. Imipenem for treatment of tuberculosis in mice and humans. Antimicrob Agents Chemother. 2005; 49: 2816–21. [PubMed: 15980354]

200. Chambers HF, Moreau D, Yajko D, et al. Can penicillins and other beta-lactam antibiotics be used to treat tuberculosis? Antimicrob Agents Chemother. 1995; 39: 2620–4. [PubMed: 8592990]

201. Sever JL, Youmans GP. The relation of oxygen tension to virulence of tubercle bacilli and to acquired resistance in tuberculosis. J Infect Dis. 1957; 101: 193–202. [PubMed: 13475878]

202. Wayne LG. The bacteriology of respected tuberculous pulmonary lesions. 2. Observations on bacilli which are stainable but which cannot be cultured. Am Rev Respir Dis. 1960; 82: 370–7. [PubMed: 13843216]

203. Aly S, Wagner K, Keller C, et al. Oxygen status of lung granulomas in *Mycobacterium tuberculosis-infected* mice. J Pathol. 2006; 210: 298–305. [PubMed: 17001607]

204. Wayne LG, Hayes LG. An in vitro model for sequential study of shiftdown of Mycobacterium tuberculosis through two stages of nonreplicating persistence. Infect Immun. 1996; 64: 2062–9. [PubMed: 8675308]

205. Andries K, Verhasselt P, Guillemont J, et al. A diarylquinoline drug active on the ATP synthase of Mycobacterium tuberculosis. Science. 2005; 307: 223–7. [PubMed: 15591164]

206. Diacon A, Pym A, Grobusch M, et al. Interim Analysis of a Double-Blind, Placebo-Controlled Study with TMC207 in Patients with Multi-Drug Resistant (MDR) Tuberculosis. ICAAC; 2008 10 25–28, 2008; Washington DC;

207. Gelber R, Andries K, Paredes RM, Andaya CE, Burgos J. The diarylquinoline R207910 is bactericidal against Mycobacterium leprae in mice at low dose and administered intermittently. Antimicrob Agents Chemother. 2009; 53: 3989–91. [PubMed: 19596891]

208. Aber VR, Nunn AJ. [Short term chemotherapy of tuberculosis. Factors affecting relapse following short term chemotherapy]. Bull Int Union Tuberc. 1978; 53: 276–80. [PubMed: 387141]

209. Benator D, Bhattacharya M, Bozeman L, et al. Rifapentine and isoniazid once a week versus rifampicin and isoniazid twice a week for treatment of drug-susceptible pulmonary tuberculosis in HIV-negative patients: a randomised clinical trial. Lancet. 2002; 360: 528–34. [PubMed: 12241657]

210. Chang KC, Leung CC, Yew WW, Ho SC, Tam CM. A nested case-control study on treatment-related risk factors for early relapse of tuberculosis. Am J Respir Crit Care Med. 2004; 170: 1124–30. [PubMed: 15374844]

211. Garton NJ, Waddell SJ, Sherratt AL, et al. Cytological and transcript analyses reveal fat and lazy persister-like bacilli in tuberculous sputum. PLoS Med. 2008; 5: e75. [PubMed: 18384229]

212. Mukamolova G, Turapov O, Malkin J, Cheah E, Barer MR. Resuscitation-promoting factor-responsive cells of *Mycobacterium tuberculosis* in human sputum samples. In: Symposia K, editor. Tuberculosis: Biology, Pathology and Therapy; 2009; Keystone, CO; 2009.

213. Wallis RS, Vinhas SA, Johnson JL, et al. Whole blood bactericidal activity during treatment of pulmonary tuberculosis. J Infect Dis. 2003; 187: 270–8. [PubMed: 12552451]

214. Diacon AH, Patientia RF, Venter A, et al. Early bactericidal activity of high-dose rifampin in patients with pulmonary tuberculosis evidenced by positive sputum smears. Antimicrob Agents Chemother. 2007; 51: 2994–6. [PubMed: 17517849]

215. Gumbo T, Siyambalapitiyage Dona CS, Meek C, Leff R. Pharmacokinetics Pharmacodynamics of Pyrazinamide In A Novel In Vitro Model of Tuberculosis for Sterilizing Effect: A Paradigm for Faster Assessment of New Antituberculosis Drugs. Antimicrob Agents Chemother. 2009.

216. Ilowite JS, Gorvoy JD, Smaldone GC. Quantitative deposition of aerosolized gentamicin in cystic fibrosis. Am Rev Respir Dis. 1987; 136: 1445–9. [PubMed: 3688646]

217. Geller DE, Pitlick WH, Nardella PA, Tracewell WG, Ramsey BW. Pharmacokinetics and bioavailability of aerosolized tobramycin in cystic fibrosis. Chest. 2002; 122: 219–26. [PubMed: 12114362]

218. Newman SP, Pellow PG, Clarke SW. Droplet size distributions of nebulised aerosols for inhalation therapy. Clin Phys Physiol Meas. 1986; 7: 139–46. [PubMed: 3720202]

219. Weber A, Morlin G, Cohen M, et al. Effect of nebulizer type and antibiotic concentration on device performance. Pediatr Pulmonol. 1997; 23: 249–60. [PubMed: 9141110]

220. Hagerman JK, Hancock KE, Klepser ME. Aerosolised antibiotics: a critical appraisal of their use. Expert Opin Drug Deliv. 2006; 3: 71–86. [PubMed: 16370941]

221. Newman SP. Aerosol deposition considerations in inhalation therapy. Chest. 1985; 88: 152S–60S. [PubMed: 3893925]

222. Cape S, Best J, Burger J, et al. Inhalable microparticles of TB antibiotics made by CAN-BD. Keystone Symposium on Tuberculosis Keystone, CO; 2009.

223. Fiegel J, Garcia-Contreras L, Thomas M, et al. Preparation and in vivo evaluation of a dry powder for inhalation of capreomycin. Pharm Res. 2008; 25: 805–11. [PubMed: 17657592]

224. Tsapis N, Bennett D, O'Driscoll K, et al. Direct lung delivery of para-aminosalicylic acid by aerosol particles. Tuberculosis (Edinb). 2003; 83: 379–85. [PubMed: 14623169]

225. Verma RK, Kaur J, Kumar K, Yadav AB, Misra A. Intracellular time course, pharmacokinetics, and biodistribution of isoniazid and rifabutin following pulmonary delivery of inhalable microparticles to mice. Antimicrob Agents Chemother. 2008; 52: 3195–201. [PubMed: 18591268]

226. Pandey R, Khuller GK. Antitubercular inhaled therapy: opportunities, progress and challenges. J Antimicrob Chemother. 2005; 55: 430–5. [PubMed: 15761077]

227. Gaspar MM, Cruz A, Fraga AG, et al. Developments on drug delivery systems for the treatment of mycobacterial infections. Curr Top Med Chem. 2008; 8: 579–91. [PubMed: 18473884]

228. Pandey R, Khuller GK. Novel delivery systems for antituberculosis drugs In: Yew WW, editor. Antituberculosis Drugs. New York: Nova Science Publishers; 2006; p. 259–75.

Table 1.

MIC, MBC and pharmacokinetic parameters of second- and third-line anti-tuberculous drugs in use or under development.

Drug	MIC [μg/ml]	MBC_{99} [1] [μg/ml]	ppb [2] %	Dose [mg/day]	T_{max} [h]	C_{max} [μg/ml]	$T_{1/2}$ [h]	AUC_t [4] [μg*h/ml]	V_{ss} or V_s/F [L/kg]	F %	References
Rifabutin	0.02	0.125	85	300	2.5–4	0.3–0.9	40–45	4	8–9	20	(35, 43)
Levofloxacin	0.5–1.0	2.0	30	500	1–2	6–10	6–8	45	1–2	>95	(44, 45)
Ofloxacin	0.5–1.2	1.0	50	400	2–3	4	4–6	48	1–2	>95	(33, 45)
Gatifloxacin	0.25–0.5	0.5	20	400	1–2	3–6	5–9	40	1–2	>95	(44, 45)
Ciprofloxacin	0.5–2.0	2.0	40	250	1–2	1.5	3–5	6	1–3	60	(45, 46)
Moxifloxacin	0.25–0.5	2.0	50	400	1–2	4–9	4–10	55	1–2	90	(44, 45, 47)
Streptomycin	2	2	35	1000	1–2	35–45	2–3	264	0.2–0.35	n/a	(48, 49)
Kanamycin	2	6	0	1000	1–2	20–45	2–4	190	0.25	n/a	(49)
Amikacin	0.5	1	0	1000	1–2	20–47	1–4	225	0.1–0.25	n/a	(33, 50)
Capreomycin	2	2.5		1000	2	35–45	4–5	400	0.25–0.4	n/a	(49)
Pyrazinamide	6	1000	35–50	1500	2	20–50	10	375	0.6–0.7	97	(49, 51)
PAS	1.5	Not cidal	50–75	4000 [3]	4–8	10–60	0.5–3	140/240 [5]	1.4	60–100	(49, 52)
D-Cycloserine	10	Not cidal	0	500	1–2	20–35	10–12	220	0.25–0.5	90	(49, 53, 54)
Ethionamide	0.3–1.2	2	30	500	2–3	2–3	1.5–3	10	1.5–4	>90	(49, 55, 56)
Prothionamide	0.3–1.2	2		750	3–4	3–4	1.3–2	12	2–3		(16, 33)
Clarithromycin	1.2–16	Not cidal	70–80	500	2–3	2–3	3–3.5	20	3–5	50	(57)
Amoxicillin / Clavulanate	2–4	4–8	25	500/250	2–4	8–10/5–7	1–1.3	24	0.3–0.4	90	(58)
Linezolid	0.5	50	30	600	2	12–14	4–7	90	0.6–1.0	99	(59, 60)
Clofazimine	0.06–2.0	1.2 [6]	70	200	4–12	0.5–2.0	7–10 days	1.5/3.7 [5]	20	60–100	(54, 61)
Metronidazole	none [7]	50 [8]	<20	3 × 500	2–4	8–22	7–10	100–160	0.6–0.9	>90	(62, 63)
TMC207	0.06	2		400	4	3–8	24	65			(64, 65)

[1] minimum concentration which results in 99% killing of laboratory strains *in vitro*

[2] human plasma protein binding

[3] granules

[4] mean values

[5] fasted / with high fat meal

[6] in macrophages due to intracellular accumulation

[7] does not inhibit growth of Mtb under standard MIC conditions

[8] only under anaerobic conditions in the Wayne model

Table 2.

Pharmacological interactions between anti-TB and other drugs.

Drug	Metabolism	CYP Induction or inhibition	DDI with TB drugs	DDI with non TB drugs	Reference
Rifabutin	demethylation and hydroxylation by CYP3A4; deacetylation by cholinesterase (deacetylation product is as active as parent)	Induces CYP3A, CYP2D and cholinesterase	CYP-mediated metabolism inhibited by CLA Induces its own metabolism	Reduces serum levels of HIV protease and reverse transcriptase inhibitors, and CYP3A4 substrates, but less so than RIF CYP-mediated metabolism inhibited by fluconazole	(81, 90, 92, 93)
Pyrazinamide	pyrazinoic acid (POA) by PZA deaminidase, and 5-OH-PA by xanthine oxidase	none clearly established			(94)
Moxifloxacin	glucuronosyltransfe rase & sulphotransferase		Co-administered RIF reduces exposure of MXF by 30%	Negligible CYP450 inhibition compared to other FQs (95)	(84–86)
Para-aminosalicylate	acetylation, glucuronide and glycine conjugation		PAS causes reduction of RIF exposure, both peak and AUC in patients, but not half life; PAS causes increased serum concentrations of INH due to inhibition of NAT-2 and competition between PAS and INH acetylation		(49, 96–98)
Clarithromycin	14-hydroxyclarithromycin by CYP3A4	Inhibits CYP3A family	CYP-mediated metabolism induced by RIF; inhibits RBT metabolism		(41, 57, 87)
Metronidazole	Likely through the P450 system, specific isomers unknown	Inhibits CYP2C9		Reduces clearance of warfarin and phenytoin. Many drug interactions described, mechanism(s) to be elucidated	(88, 99)
Linezolid	morpholine ring oxidation - CYP450-independent	No interaction with CYP system demonstrated; induces monoamine oxidase (MAO)		Potential interaction with adrenergic (tyramine) and serotonergic agents, leading to hypertensive crises and serotonin syndrome due to MAO induction.	(59)
TMC207	By CYP3A4		Clearance increased by RIF resulting in 50% reduction of exposure		(89)

Table 3.

Summary of INH and RIF concentrations in blood, lung tissue and various lesion compartments[1]

Tissue	Blood	Healthy lung	bronchopulmonary lymph nodes	cavities	Tuberculous foci	Tuberculom as	caseous lymph nodes
Units	μg/mL	μg/g	μg/g	μg/g	μg/g	μg/g	μg/g
RIF alone	6.95	2.22	1.41	1.03	2.43	0.18	0.03
RIF in combination with INH	1.1	0.99	0.72	0.39	0.3	0.12	0.03
INH alone	4.11	0.58	0.53	0.59	0.6	0.49	0.21
INH in combination with RIF	3.3	0.96	0.42	0.21	0.45	0.29	0.02

[1] translated and adapted from (109)

Table 4.

Exposure ratio of some second- and third-line drugs in bronchial compartments versus plasma and in intracellular space

Drug	Sputum : plasma	ELF : plasma	AM : plasma	IC : EC[1]	Mw	cLogP	References
Rifabutin		nd	nd	9	847.0	6.3	(35)
Moxifloxacin		5–7	20–70	7–15[2]	437.9	0.6	(125, 126)
Levofloxacin		2	5–10	7–10	361.4	−0.4	(126–128)
Aminoglycoside[3]	0.1–0.2[4]	0.10–0.13		2–5[5]	low	−7.3	(115, 116)
Ethionamide		8–10	0.5	Low	166.2	1.1	(129)
Pyrazinamide		20	0.5–1.0	1–3	123.1	−0.6	(130, 131)
Linezolid	1	3–4	0.1–0.2	0.5	337.4	0.7	(126, 132, 133)
Clarithromycin		10–30[6]	200–1200		748.0	3.2	(132, 134, 135)
Amoxicillin	0.05–0.1	0.15	none detected	~ 0	365.4	−2	(136–141)
TMC207	3–5				555.50	7.2	(97)

nd: not determined

[1] intracellular to extracellular ratio

[2] accumulation is higher, around 45-fold, in differentiated macrophages (120)

[3] tobramycin given i.v. to cystic fibrosis patients, in the absence of any data for AGs used against TB

[4] after single dose; accumulation to higher ratios seen after 2–3 weeks of daily i.v. administration

[5] in rat fibroblasts (142) and mouse macrophages (143)

[6] free CLA levels in soft tissue, measured by microdialysis, provided 0.5 tissue-to-free-plasma drug ratio (144)

Table 5.

Early bactericidal activity of some second- and third-line drugs expressed as mean Δlog CFU/mL sputum/day

Drug (daily dose in mg)	Day 0–2	Day 2–7	Reference
Isoniazid (300)	0.5 to 0.7	0.1 to 0.2	(148)[1]
Rifabutin (600)	0.05 to 0.075	nd	(149, 150)
Levofloxacin (1000)	0.45	0.18	(151)
Gatifloxacin (400)	0.35	0.17	(151)
Moxifloxacin (400)	0.33	0.17	(151)
Amikacin (300–750)	0.04 – 0.05	nd	(118)
Streptomycin (7501500)	0.04 – 0.133	nd	(152)
Pyrazinamide (2000)	0.003 to 0.05	0.04	(145, 153, 154)
Amoxicillin / Clavulanate 1 × 3000/750	0.018	nd	(155, 156)
3 × 1000/250	0.34	0.02	
Linezolid (600)	0.18	0.09	(157)
TMC207	0	0.15	(64)

nd: not determined

[1]Used as positive control in most studies listed and included here as a reference compound